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(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of the following applications: Ser. No. 08/677,231, filed July 9, 1996; Ser. No. 08/701,819, filed August 23, 1996; Ser. No. 08/721,488, filed September 27, 1996; and Ser. No. 08/739,066, filed October 28, 1996.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising

an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1

from nucleotide 179 to nucleotide 742; the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568; the nucleotide sequence of the full-length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:3 from nucleotide 218 to nucleotide 1126;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553; the nucleotide sequence of the full-length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited

under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994; the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994; the nucleotide sequence of the full-length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising

a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204; the nucleotide sequence of the full-length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:9 from nucleotide 1 to nucleotide 323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323; the nucleotide sequence of the full-length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731; the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186; the nucleotide sequence of the full-length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125;

(c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708; the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890; the nucleotide sequence of the full-length protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180; or the nucleotide sequence of the mature protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) fragments of the amino acid sequence of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 51 to nucleotide 1319;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:15 from nucleotide 126 to nucleotide 1319;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 51 to nucleotide 1319; the nucleotide sequence of SEQ ID NO:15 from nucleotide 126 to nucleotide 1319; the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495; the nucleotide sequence of the full-length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by

the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) fragments of the amino acid sequence of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid

sequence of SEQ ID NO:19;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350; the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350; the nucleotide sequence of the full-length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:19.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774; the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477; the nucleotide sequence of the full-length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101. In other preferred

embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;

(c) fragments of the amino acid sequence of SEQ ID NO:22; and

(d) the amino acid sequence encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22 or the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;

(e) a polynucleotide encoding the full-length protein encoded by the

cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801; the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421; the nucleotide sequence of the full-length protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152; or the nucleotide sequence of the mature protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:23.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:24;

(b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;

(c) fragments of the amino acid sequence of SEQ ID NO:24; and

(d) the amino acid sequence encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:24 or the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the

cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 812 to nucleotide 886; the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853; the nucleotide sequence of the full-length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:25.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:26;

(b) fragments of the amino acid sequence of SEQ ID NO:26; and

(c) the amino acid sequence encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:26.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609; the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483; the nucleotide sequence of the full-length

protein coding sequence of clone O289_1 deposited under accession number ATCC 98101; or the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:27.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:28;

(b) fragments of the amino acid sequence of SEQ ID NO:28; and

(c) the amino acid sequence encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:28.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically

effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1A and Fig. 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

Fig. 2 is an autoradiograph evidencing the expression of the following clone disclosed herein, BG33_7.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "AC41_1"

A polynucleotide of the present invention has been identified as clone "AC41_1".

AC41_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC41_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC41_1 protein").

The nucleotide sequence of AC41_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC41_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2. Amino acids 10 to 22 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 23, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC41_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AC41_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC41_1 demonstrated at least some homology with sequences identified as L20319 (Rattus norvegicus developmentally regulated protein mRNA, complete cds), U46493 (Cloning vector pFlp recombinase gene, complete cds), and Z22650 (H.sapiens insertion polymorphism DNA). The predicted amino acid sequence disclosed herein for AC41_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AC41_1 protein demonstrated at least some identity with sequences identified as L20319 (developmentally regulated protein [Rattus norvegicus]) and X12544 (3 HLA-DR B protein precursor (AA -29 to 267) [Homo sapiens]). Based upon homology, AC41_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AC222_1"

A polynucleotide of the present invention has been identified as clone "AC222_1". AC222_1 was isolated from a human adult placenta cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No.

5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AC222_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AC222_1 protein").

The nucleotide sequence of AC222_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AC222_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 7 to 19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AC222_1 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for AC222_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AC222_1 demonstrated at least some homology with sequences identified as D10485 (Chicken mRNA for proteoglycan (PG-Lb) core protein, complete cds), D78274 (Mouse mRNA for proteoglycan, complete cds), N22463 (yw34c10.s1 Homo sapiens cDNA clone 254130 3'), U59111 (Human dermatan sulfate proteoglycan 3 (DSPG3) mRNA, complete cds), U77127 (Bos taurus epiphycan mRNA, complete cds), and Z32693 (E.coli pT7hGH_pl DNA, 6160bp). The predicted amino acid sequence disclosed herein for AC222_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AC222_1 protein demonstrated at least some identity with sequences identified as D10485 (proteoglycan core protein [Gallus gallus]), D78274 (proteoglycan [Mus musculus]), U77127 (epiphycan [Bos taurus]), and U59111 (dermatan sulfate proteoglycan 3 [Homo sapiens]). Based upon homology, AC222_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AJ143_1"

A polynucleotide of the present invention has been identified as clone "AJ143_1". AJ143_1 was isolated from a human adult testes cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ143_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ143_1 protein").

The nucleotide sequence of AJ143_1 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AJ143_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 2 to 14 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 15, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ143_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AJ143_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ143_1 demonstrated at least some homology with sequences identified as T19431 (d08002s Homo sapiens cDNA clone d08002 5' end) and Z41997 (H. sapiens partial cDNA sequence; clone c-05c07); it may also show some similarity to phosphoenolpyruvate phosphomutase. Based upon homology, AJ143_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "AJ168_4"

A polynucleotide of the present invention has been identified as clone "AJ168_4". AJ168_4 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AJ168_4 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AJ168_4 protein").

The nucleotide sequence of AJ168_4 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the AJ168_4 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AJ168_4 should be approximately 700 bp.

The nucleotide sequence disclosed herein for AJ168_4 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AJ168_4 demonstrated at least some homology with sequences identified as T65223 (yc79c02.s1 Homo sapiens cDNA clone 22106 3'). Based upon homology, AJ168_4 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AJ168_4 protein sequence (SEQ ID NO:8).

Clone "AK684_1"

A polynucleotide of the present invention has been identified as clone "AK684_1". AK684_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AK684_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AK684_1 protein").

The nucleotide sequence of AK684_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AK684_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AK684_1 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for AK684_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AK684_1 demonstrated at least some homology with sequences identified as AA226405 (nc20c05.r1 NCI CGAP Pr1 Homo sapiens cDNA clone 2817), G15531 (human STS SHGC-17023), and T68858 (yc30d08.s1 Homo sapiens

cDNA clone 82191 3' similar to contains MSR1 repetitive element). Based upon homology, AK684_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AK684_1 protein sequence centered around amino acid 20 of SEQ ID NO:10.

Clone "AS209_1"

A polynucleotide of the present invention has been identified as clone "AS209_1". AS209_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AS209_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AS209_1 protein").

The nucleotide sequence of AS209_1 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AS209_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Amino acids 32 to 44 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 45, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AS209_1 should be approximately 2882 bp.

The nucleotide sequence disclosed herein for AS209_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AS209_1 demonstrated at least some homology with sequences identified as AA055217 (zf17h02.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 377235 3') and H29533 (ym60h11.r1 Homo sapiens cDNA clone 52955 5' similar to SP:A60164 S34329; PLATELET MEMBRANE GLYCOPROTEIN V PRECURSOR). The predicted amino acid sequence disclosed herein for AS209_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AS209_1 protein demonstrated at least some

identity with sequences identified as D63875 (ORF [Homo sapiens]) and X53959 (slit protein [Drosophila melanogaster]). Based upon homology, AS209_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AS209_1 protein sequence, centered around amino acids 32, 387, 449, and 538 of SEQ ID NO:12.

Clone "AX56_28"

A polynucleotide of the present invention has been identified as clone "AX56_28". AX56_28 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX56_28 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX56_28 protein").

The nucleotide sequence of AX56_28 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX56_28 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX56_28 should be approximately 4500 bp.

The nucleotide sequence disclosed herein for AX56_28 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX56_28 demonstrated at least some homology with sequences identified as M20816 (Chicken cytotactin mRNA, partial cds, clone pEC803 [Gallus gallus]), N67571 (yz42a06.s1 Homo sapiens cDNA clone 285682 3'), and T19080 (e05023t Testis 1 Homo sapiens cDNA clone e05023 5' end). The predicted amino acid sequence disclosed herein for AX56_28 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AX56_28 protein demonstrated at least some identity with sequences identified as L12018 (putative protein [Caenorhabditis elegans]). Based upon homology, AX56_28 proteins and each homologous protein or peptide may share at least some activity. The

TopPredII computer program predicts a potential transmembrane domain within the AX56_28 protein sequence (SEQ ID NO:14).

Clone "AX92_3"

A polynucleotide of the present invention has been identified as clone "AX92_3". AX92_3 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AX92_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AX92_3 protein").

The nucleotide sequence of AX92_3 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AX92_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 13 to 25 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 26, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AX92_3 should be approximately 1800 bp.

The nucleotide sequence disclosed herein for AX92_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AX92_3 demonstrated at least some homology with sequences identified as AA003356 (mg49g01.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 427152 5'), AA036247 (mi74a03.r1 Soares mouse p3NMF19.5 Mus musculus cDNA clone 472300 5'), F19608 (H.sapiens mitochondrial EST sequence (009-X4-35) from skeletal muscle), M10546 (Human mitochondrial DNA, fragment M1, encoding transfer RNAs, cytochrome oxidase I, and 2 URFs [Mitochondrion Homo sapiens]), and U46493 (Cloning vector pFlp recombinase gene, complete cds). Based upon homology, AX92_3 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts four potential transmembrane domains within the AX92_3 protein sequence, centered around amino

acids 20, 183, 269, and 295 of SEQ ID NO:16.

Clone "BF245_1"

A polynucleotide of the present invention has been identified as clone "BF245_1". BF245_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BF245_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BF245_1 protein").

The nucleotide sequence of the 5' portion of BF245_1 as presently determined is reported in SEQ ID NO:17. An additional internal nucleotide sequence from BF245_1 as presently determined is reported in SEQ ID NO:18. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:19. Amino acids 18 to 30 of SEQ ID NO:19 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 31, or are a transmembrane domain. Additional nucleotide sequence from the 3' portion of BF245_1, including the polyA tail, is reported in SEQ ID NO:20.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BF245_1 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for BF245_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BF245_1 demonstrated at least some homology with sequences identified as AA001743 (zh86h02.s1 Soares fetal liver spleen 1NFLS S1 Homo sapiens cDNA clone 428211 3' similar to SW YY02_HUMAN P42285 HYPOTHETICAL MYELOID CELL LINE PROTEIN 2), D29641 (Human mRNA for KIAA0052 gene, partial cds), Q92779 (Human thymopoietin continuous gene fragment), and R39256 (yc91h04.s1 Homo sapiens cDNA clone 23509 3'). The predicted amino acid sequence disclosed herein for BF245_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BF245_1 protein

demonstrated at least some identity with sequences identified as Z70271 (W08D2.7 [Caenorhabditis elegans]). Based upon homology, BF245_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "BG33_7"

A polynucleotide of the present invention has been identified as clone "BG33_7". BG33_7 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BG33_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG33_7 protein").

The nucleotide sequence of BG33_7 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BG33_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG33_7 should be approximately 900 bp.

The nucleotide sequence disclosed herein for BG33_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BG33_7 demonstrated at least some homology with sequences identified as AA033818 (zf02c08.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 375758 3') and AA462657 (vg68e04.r1 Soares mouse NbMH Mus musculus cDNA clone 871134 5'). Based upon homology, BG33_7 proteins and each homologous protein or peptide may share at least some activity.

Fig. 2 is an autoradiograph evidencing expression in COS cells of clone BG33_7 of the present invention.

Clone "BM46_10"

A polynucleotide of the present invention has been identified as clone "BM46_10". BM46_10 was isolated from a human adult muscle cDNA library using

methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BM46_10 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BM46_10 protein").

The nucleotide sequence of BM46_10 as presently determined is reported in SEQ ID NO:23. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BM46_10 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:24.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BM46_10 should be approximately 3600 bp.

The nucleotide sequence disclosed herein for BM46_10 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BM46_10 demonstrated at least some homology with sequences identified as F19321 (H.sapiens EST sequence 008-X (391 nt)), N79027 (zb43c09.s1 Homo sapiens cDNA clone 306352 3'), U46493 (Cloning vector pFlp recombinase gene, complete cds), and W74198 (zd74d05.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 346377 3'). Based upon homology, BM46_10 proteins and each homologous protein or peptide may share at least some activity.

Clone "J317_1"

A polynucleotide of the present invention has been identified as clone "J317_1". J317_1 was isolated from a human peripheral blood mononuclear cells (treated with phytohemagglutinin and phorbol myristate acetate and mixed lymphocyte reaction) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. J317_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J317_1 protein").

The nucleotide sequence of J317_1 as presently determined is reported in SEQ ID NO:25. What applicants presently believe to be the proper reading frame and the

predicted amino acid sequence of the J317_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:26. Amino acids 19 to 31 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone J317_1 should be approximately 1300 bp.

The nucleotide sequence disclosed herein for J317_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. J317_1 demonstrated at least some homology with sequences identified as N21491 (yx58f09.s1 Homo sapiens cDNA clone 265961 3'), R39024 (yd08h03.s1 Homo sapiens cDNA clone 25214 3'), T93953 (ye06h06.r1 Homo sapiens cDNA clone 116987 5' similar to contains HGR repetitive element), and Z25379 (H. sapiens partial cDNA sequence; clone C6F07; version 1; strand(+), single read). Based upon homology, J317_1 proteins and each homologous protein or peptide may share at least some activity.

Clone "O289_1"

A polynucleotide of the present invention has been identified as clone "O289_1". O289_1 was isolated from a human adult blood (dendritic cells) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. O289_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "O289_1 protein").

The nucleotide sequence of O289_1 as presently determined is reported in SEQ ID NO:27. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the O289_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:28.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone O289_1 should be approximately 700 bp.

The nucleotide sequence disclosed herein for O289_1 was searched against the

GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. O289_1 demonstrated at least some homology with sequences identified as H59298 (yr04c07.r1 Homo sapiens cDNA clone 204300 5' similar to contains MER22 repetitive element). Based upon homology, O289_1 proteins and each homologous protein or peptide may share at least some activity. The TopPredII computer program predicts a large potential transmembrane domain within the O289_1 protein sequence, centered around amino acid 35 of SEQ ID NO:28. The nucleotide/amino acid sequence of O289_1 indicates that it may contain MER transposon repetitive elements.

Deposit of Clones

Clones AC41_1, AC222_1, AJ143_1, AJ168_4, AK684_1, AS209_1, AX92_3, BF245_1, BG33_7, J317_1 and O289_1, along with AX56_8 and BM46_3 (additional isolates of clones AX56_28 and BM46_10, respectively), were deposited on July 9, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98101, from which each clone comprising a particular polynucleotide is obtainable. AX56_28 was deposited on September 26, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98180; BM46_10 was deposited on August 23, 1996 with the American Type Culture Collection as an original deposit under the Budapest Treaty and was given the accession number ATCC 98152. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1A or Fig. 1B, respectively. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* 19: 4485-4490); the pNOTs vector was derived from

pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* 9: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
AC41_1	SEQ ID NO:29
AC222_1	SEQ ID NO:30
AJ143_1	SEQ ID NO:31
AJ168_4	SEQ ID NO:32
AK684_1	SEQ ID NO:33
AS209_1	SEQ ID NO:34
AX56_28	SEQ ID NO:35
AX92_3	SEQ ID NO:36
BF245_1	SEQ ID NO:37
BG33_7	SEQ ID NO:38
BM46_10	SEQ ID NO:39
J317_1	SEQ ID NO:40
O289_1	SEQ ID NO:41

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0

with NaOH) containing 0.5% SDS, 100 μg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be

determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which the cDNA sequences are derived and any contiguous regions of the genome necessary for the regulated expression of such genes, including but not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides .

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such

as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or

thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or

replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel

polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-

3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai

et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing

T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy

in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science *257*:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the

common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a

cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In*

vitro antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood

85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include,

without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also

is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of

central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon);

International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity.

As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek,

D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate

antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following

additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The

pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a

liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful

therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of

the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering

various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 113 to nucleotide 742;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 179 to nucleotide 742;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 1 to nucleotide 568;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC41_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein, which comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying the protein from the culture.

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC41_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 53 to amino acid 129.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 161 to nucleotide 1126;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 218 to nucleotide 1126;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 553;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AC222_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 131;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone AC222_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 827 to nucleotide 994;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 869 to nucleotide 994;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ143_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 20;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone AJ143_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 91 to nucleotide 204;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AJ168_4 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) fragments of the amino acid sequence of SEQ ID NO:8; and

(c) the amino acid sequence encoded by the cDNA insert of clone AJ168_4 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 60 to nucleotide 230;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 323;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AK684_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the

amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) fragments of the amino acid sequence of SEQ ID NO:10; and

(c) the amino acid sequence encoded by the cDNA insert of clone AK684_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 812 to nucleotide 2731;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 944 to nucleotide 2731;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 855 to nucleotide 1186;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AS209_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 1 to amino acid 125;

(c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone AS209_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 2196 to nucleotide 2708;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 489 to nucleotide 890;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX56_28 deposited under accession number ATCC 98180;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) fragments of the amino acid sequence of SEQ ID NO:14; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX56_28 deposited under accession number ATCC 98180;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 51 to nucleotide 1319;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 126 to nucleotide 1319;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 409 to nucleotide 495;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AX92_3 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) fragments of the amino acid sequence of SEQ ID NO:16; and

(c) the amino acid sequence encoded by the cDNA insert of clone AX92_3 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 210 to nucleotide 350;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:18 from nucleotide 300 to nucleotide 350;

(d) a polynucleotide comprising the nucleotide sequence of the full-

length protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BF245_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:19;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:19 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:19;

(b) fragments of the amino acid sequence of SEQ ID NO:19; and

(c) the amino acid sequence encoded by the cDNA insert of clone BF245_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:18, SEQ ID NO:17 or SEQ ID NO:20 .

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 322 to nucleotide 774;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 149 to nucleotide 477;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG33_7 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) the amino acid sequence of SEQ ID NO:22 from amino acid 1 to amino acid 121;

(c) fragments of the amino acid sequence of SEQ ID NO:22; and

(d) the amino acid sequence encoded by the cDNA insert of clone BG33_7 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:21.

41. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 80 to nucleotide 1801;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:23 from nucleotide 1 to nucleotide 421;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BM46_10 deposited under accession number ATCC 98152;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:24;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:24 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

42. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:24;

(b) the amino acid sequence of SEQ ID NO:24 from amino acid 1 to amino acid 112;

(c) fragments of the amino acid sequence of SEQ ID NO:24; and

(d) the amino acid sequence encoded by the cDNA insert of clone BM46_10 deposited under accession number ATCC 98152;

the protein being substantially free from other mammalian proteins.

43. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:23.

44. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 719 to nucleotide 886;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID

NO:25 from nucleotide 812 to nucleotide 886;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:25 from nucleotide 1 to nucleotide 853;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J317_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:26;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:26 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

45. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:26;

(b) fragments of the amino acid sequence of SEQ ID NO:26; and

(c) the amino acid sequence encoded by the cDNA insert of clone J317_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

46. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:25.

47. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 442 to nucleotide 609;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:27 from nucleotide 1 to nucleotide 483;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone O289_1 deposited under accession number ATCC 98101;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:28;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:28 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

48. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:28;

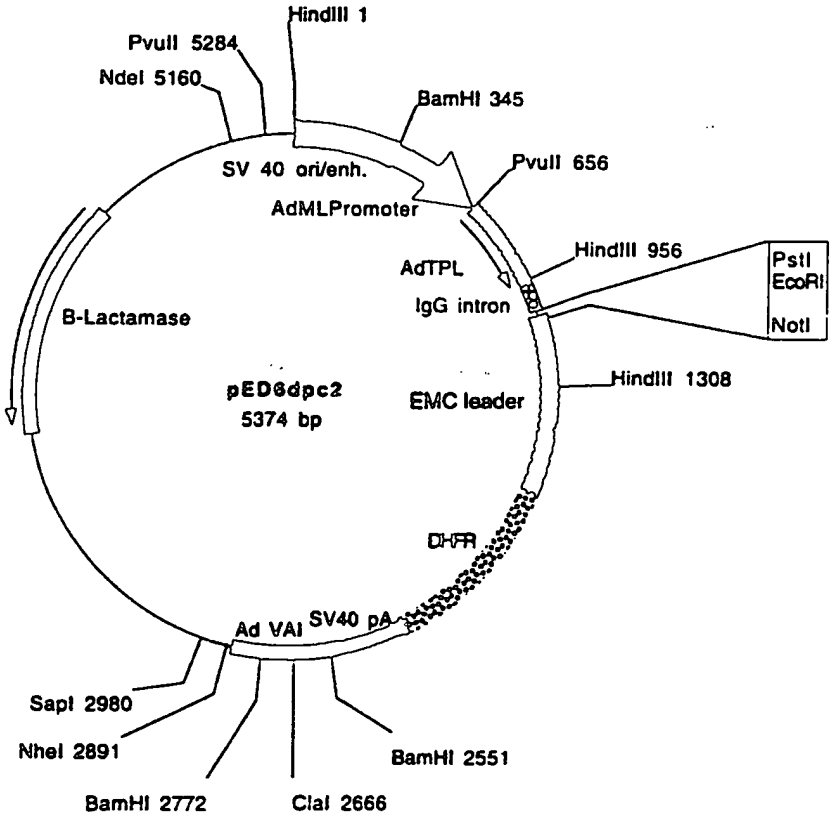
(b) fragments of the amino acid sequence of SEQ ID NO:28; and

(c) the amino acid sequence encoded by the cDNA insert of clone O289_1 deposited under accession number ATCC 98101;

the protein being substantially free from other mammalian proteins.

49. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:27.

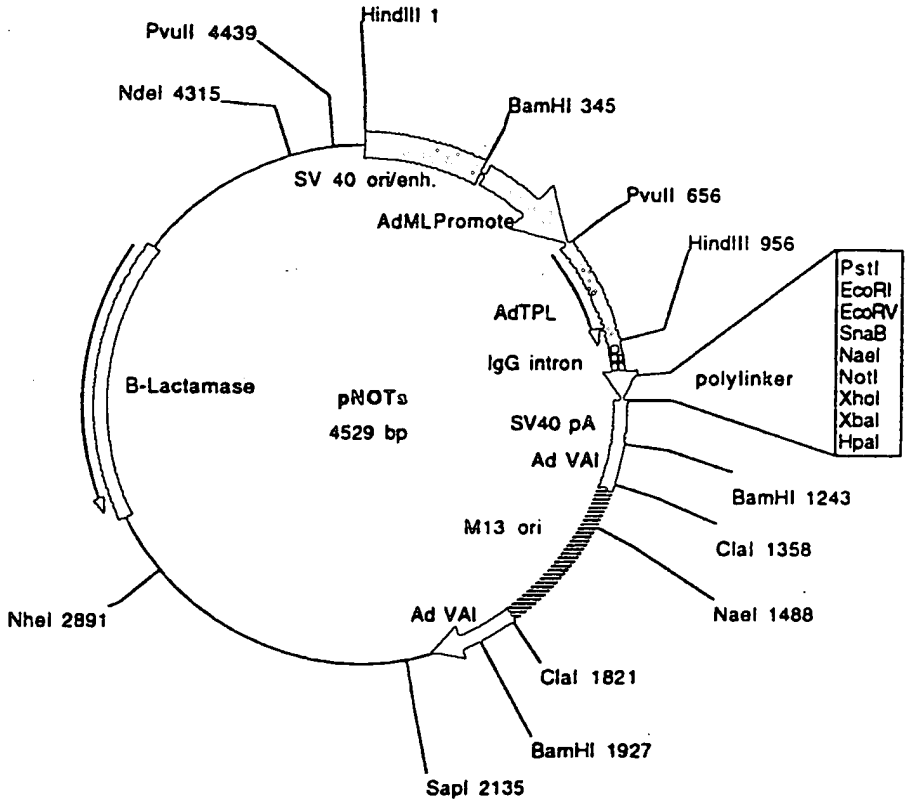
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI

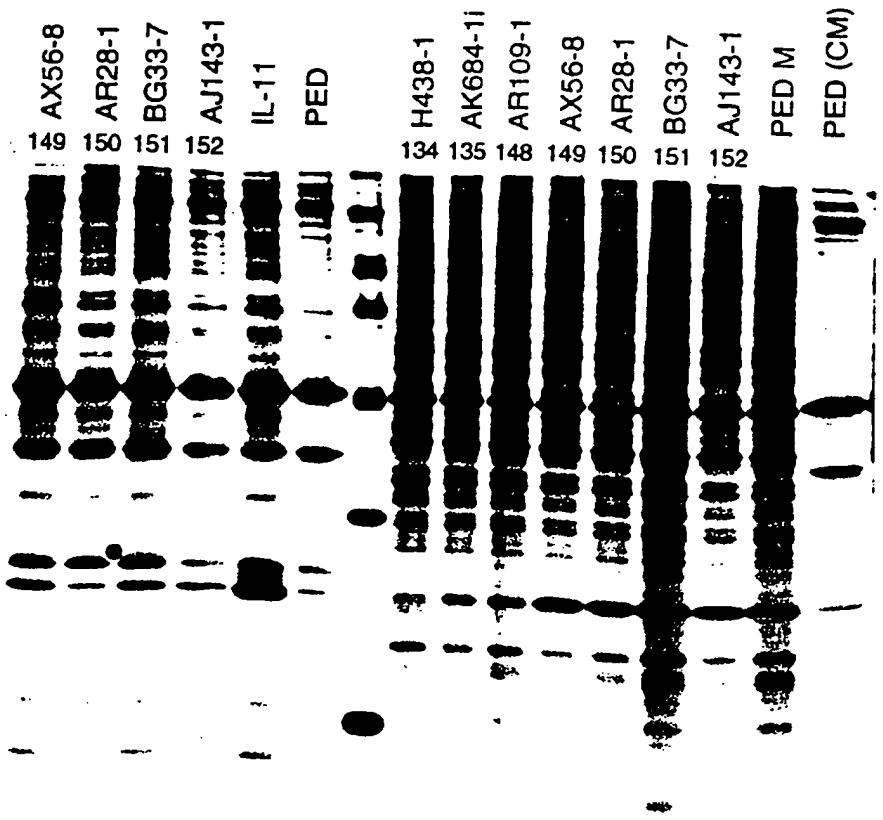

AX56-8
149
AR28-1
150
BG33-7
151
AJ143-1
152
IL-11
PED
H438-1
134
AK684-1i
135
AR109-1
148
AX56-8
149
AR28-1
150
BG33-7
151
AJ143-1
152
PED M
PED (CM)

FIGURE 2

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Merberg, David
Treacy, Maurice
Evans, Cheryl
Spaulding, Vikki
Bowman, Michael
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 41

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: U.S.A.
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Sprunger, Suzanne A.
(B) REGISTRATION NUMBER: 41,323

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617) 498-8284
(B) TELEFAX: (617) 876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1032 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CTTCGTTCAA GTGTGAGCTG CGGCTGAGCC CAGCGCTCGA GGCGCGAGGC AGCCAGGAGG 60

GCCCGTGCGG CGCGGGGAGC CAGCGAGCGC GCCTTCGGCA TTGGCCGCCG CGATGTCAGC 120

TCAGTGCTGT GCGGGCCACC TGGCCTGCTG CTGTGGGTCT GCAGGCTGCT CTCTCTGCTG 180

TGATTGCTGC CCCAGGATTC GGCAGTCCCT CAGCACCCGC TTCATGTACG CCCTCTACTT 240

CATTCTGGTC GTCGTCCTCT GCTGCATCAT GATGTCAACA ACCGTGGCTC ACAAGATGAA 300

AGAGCACATT CCTTTTTTTG AAGATATGTG TAAAGGCATT AAAGCTGGTG ACACCTGTGA 360

GAAGCTGGTG GGATATTCTG CCGTGTATAG AGTCTGTTTT GGAATGGCTT GTTTCTTCTT 420

TATCTTCTGT CTACTGACCT TGAAAATCAA CAACAGCAAA AGTTGTAGAG CTCATATTCA 480

CAATGGCTTT TGGTTCTTTA AACTTCTGCT GTTGGGGGCC ATGTGCTCAG GAGCTTTCTT 540

CATTCCAGAT CAGGACACCT TTCTGAACGC CTGGCGCTAT GTGGGAGCCG TCGGAGGCTT 600

CCTCTTCATT GGCATCCAGT CCTCCTGCTC GTGGAGTTTG CACATAAGTG GAACAAGAAC 660

TGGTGTGTGC CTTTATGGAA AGCTTCCCAT TGACTCACAG AAACTGCCCA GTTTTGACCA 720

AGGCTGTACT CAACTGCATT GCTAGGGATT TGCAGTTTTG TTTCCCTTTA TACCTGCTTT 780

TTTGTACCTC TTCATATACT CCTCTCCTTC ATTCACTTCT CACTTTTTGA CCCCCTGCCC 840

CTACTCCCTT GCTTGGGCTC TGAGTCAACC AGTGGTGTGA ATTAGCCACA CTCAATCCCC 900

TGCTCGTACG GGTCTCGATC TCCTGACCTC GTGATCCGCC CACCTCGGCC TCCCAAAGTG 960

CTGGGATTAC AGGCTCGAGC CACCGCACCT GGCCTGATGD TTCTGCAAAA AAAAAAAAAA 1020

AAAAAAAAAA AA 1032

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 210 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Met Ser Ala Gln Cys Cys Ala Gly His Leu Ala Cys Cys Cys Gly Ser
1               5                  10                  15

Ala Gly Cys Ser Leu Cys Cys Asp Cys Cys Pro Arg Ile Arg Gln Ser
            20                  25                  30

Leu Ser Thr Arg Phe Met Tyr Ala Leu Tyr Phe Ile Leu Val Val Val
        35                  40                  45

Leu Cys Cys Ile Met Met Ser Thr Thr Val Ala His Lys Met Lys Glu
    50                  55                  60

His Ile Pro Phe Phe Glu Asp Met Cys Lys Gly Ile Lys Ala Gly Asp
65                  70                  75                  80

Thr Cys Glu Lys Leu Val Gly Tyr Ser Ala Val Tyr Arg Val Cys Phe
                85                  90                  95

Gly Met Ala Cys Phe Phe Phe Ile Phe Cys Leu Leu Thr Leu Lys Ile
            100                 105                 110

Asn Asn Ser Lys Ser Cys Arg Ala His Ile His Asn Gly Phe Trp Phe
        115                 120                 125

Phe Lys Leu Leu Leu Leu Gly Ala Met Cys Ser Gly Ala Phe Phe Ile
    130                 135                 140

Pro Asp Gln Asp Thr Phe Leu Asn Ala Trp Arg Tyr Val Gly Ala Val
145                 150                 155                 160

Gly Gly Phe Leu Phe Ile Gly Ile Gln Ser Ser Cys Ser Trp Ser Leu
                165                 170                 175

His Ile Ser Gly Thr Arg Thr Gly Val Cys Leu Tyr Gly Lys Leu Pro
            180                 185                 190

Ile Asp Ser Gln Lys Leu Pro Ser Phe Asp Gln Gly Cys Thr Gln Leu
        195                 200                 205

His Cys
    210
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1626 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGGGCCAGGT TTTCCGGGCC NTCACATTGC CAAAAGACGG CAATATGGTG GGAAATAACA 60

TATAGACAAA CGCACACCGG CCTTATTCCA AGCGGNTTCG GCCAGTAACG TTAGAATTGC 120

GGCCGCAGGT YTAGGTCAGA GCCAAAGGAA AGCTTGAAAA ATGAAGACAT TAGCAGGACT 180

TGTTCTGGGA CTTGTCATCT TTGATGCTGC TGTGACTGCC CCAACTCTAG AGTCCATCAA 240

CTATGACTCA GAAACCTATG ATGCCACCTT AGAAGACCTG GATAATTTGT ACAACTATGA 300

AAACATACCT GTTGATAAAG TTGAGATTGA AATAGCCACA GTGATGCCTT CAGGGAACAG 360

AGAGCTCCTC ACTCCACCCC CACAGCCTGA GAAGGCCCAG GAAGAGGAAG AGGAGGAGGA 420

ATCTACTCCC AGGCTGATTG ATGGCTCTTC TCCCCAGGAG CCTGAATTCA CAGGGGTTCT 480

GGGGCCACAC ACAAATGAAG ACTTTCCAAC CTGTCTTTTG TGTACTTGTA TAAGTACCAC 540

CGTGTACTGT GATGACCATG AACTTGATGC TATTCCTCCG CTGCCAAAGA ACACCGCTTA 600

TTTCTATTCC CGCTTTAACA GAATTAAAAA GATCAACAAA AATGACTTTG CAAGCCTAAG 660

TGATTTAAAA AGGATTGATC TGACATCAAA TTTAATATCT GAGATTGATG AAGATGCATT 720

CCGAAAACTG CCTCAACTTC GAGAGCTTGT CCTGCGTGAC AACAAAATAA GGCAGCTCCC 780

AGAATTGCCA ACCACTTTGA CATTTATTGA TATTAGCAAC AATAGACTTG GAAGGAAAGG 840

GATAAAGCAA GAAGCATTTA AAGACATGTA TGATCTCCAT CATCTGTACC TCACTGATAA 900

CAACTTGGAC CACATCCCTC TGCCACTCCC AGAAAATCTA CGAGCCCTTC ACCTCCAGAA 960

TAACAACATT CTGGAAATGC ACGAAGATAC GTTCTGCAAT GTTAAAAATT TGACTTATAT 1020

TCGTAAGGCA CTAGAGGACA TTCGATTGGA TGGAAACCCT ATTAATCTCA GCAAAACTCC 1080

TCAAGCATAC ATGTGTCTAC CTCGTCTGCC TGTTGGGAGC CTTGTCTAAT TTCAGATAAT 1140

GGTTAGCATT ACGATGGCTA CTATAAATAA ACCATTCTTA CTGCTCTCTT CCAAAACAAA 1200

ACTCAGCATG ATACTTTGAG ATTGTGTTCT GAGAGATGAT ATGACTACAT AAAATACAAT 1260

TAAAAATGTT ATAATATAAT GAAAATGTAG TAATTTAAGA AAACACCAGA TGAGTTAGGA 1320

ATAAACCTAT AACATTTACA AAAAGAGCAA AAYTAAGTGA TAGAAAATAT TTCACACATG 1380

TTCTTATAGA TCATGTATCA CTTGCAAGTT TTAGGAGTTC ATATCCTATA TCATTTCAAA 1440

TTAAGTACAT AATAAAGTAA AATTTTGAAA TGAACACTTT AGGTATTTTT GCCAAGATTT 1500

AGATGTTTTT AATTAAACTT TTYTCTTCCT TTTTTTTTCA CTAAAGCATG TTTATTCCCC 1560

TAATCCATTA AAGAGCATGA AAAAAAGAAT AAATGTATTT GAAAATTAAA AAAAAAAAAA 1620

AAAAAA 1626

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 322 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Lys Thr Leu Ala Gly Leu Val Leu Gly Leu Val Ile Phe Asp Ala
1 5 10 15

Ala Val Thr Ala Pro Thr Leu Glu Ser Ile Asn Tyr Asp Ser Glu Thr
20 25 30

Tyr Asp Ala Thr Leu Glu Asp Leu Asp Asn Leu Tyr Asn Tyr Glu Asn
35 40 45

Ile Pro Val Asp Lys Val Glu Ile Glu Ile Ala Thr Val Met Pro Ser
50 55 60

Gly Asn Arg Glu Leu Leu Thr Pro Pro Pro Gln Pro Glu Lys Ala Gln
65 70 75 80

Glu Glu Glu Glu Glu Glu Glu Ser Thr Pro Arg Leu Ile Asp Gly Ser
85 90 95

Ser Pro Gln Glu Pro Glu Phe Thr Gly Val Leu Gly Pro His Thr Asn
100 105 110

Glu Asp Phe Pro Thr Cys Leu Leu Cys Thr Cys Ile Ser Thr Thr Val
115 120 125

Tyr Cys Asp Asp His Glu Leu Asp Ala Ile Pro Pro Leu Pro Lys Asn
130 135 140

Thr Ala Tyr Phe Tyr Ser Arg Phe Asn Arg Ile Lys Lys Ile Asn Lys
145 150 155 160

Asn Asp Phe Ala Ser Leu Ser Asp Leu Lys Arg Ile Asp Leu Thr Ser
165 170 175

Asn Leu Ile Ser Glu Ile Asp Glu Asp Ala Phe Arg Lys Leu Pro Gln

180 185 190

Leu Arg Glu Leu Val Leu Arg Asp Asn Lys Ile Arg Gln Leu Pro Glu
195 200 205

Leu Pro Thr Thr Leu Thr Phe Ile Asp Ile Ser Asn Asn Arg Leu Gly
210 215 220

Arg Lys Gly Ile Lys Gln Glu Ala Phe Lys Asp Met Tyr Asp Leu His
225 230 235 240

His Leu Tyr Leu Thr Asp Asn Asn Leu Asp His Ile Pro Leu Pro Leu
245 250 255

Pro Glu Asn Leu Arg Ala Leu His Leu Gln Asn Asn Asn Ile Leu Glu
260 265 270

Met His Glu Asp Thr Phe Cys Asn Val Lys Asn Leu Thr Tyr Ile Arg
275 280 285

Lys Ala Leu Glu Asp Ile Arg Leu Asp Gly Asn Pro Ile Asn Leu Ser
290 295 300

Lys Thr Pro Gln Ala Tyr Met Cys Leu Pro Arg Leu Pro Val Gly Ser
305 310 315 320

Leu Val

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1083 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CWAAAACATG AGACCWRGGC WCAGACCTTA CTGTATGAGA AGCAATGCTC CTCAAACCTT 60

CTGCGTGCTG ACATAGACCT TCCCARAAGC WAAACTGTTG GCGGCGACCT GAGCGCTGGA 120

AGCCGAAGGG GAAGAGGAGG GAGACGCGAA GCCAGGGCGG YCGGCACWWA GGCGGCGGAC 180

TCGCGGSGGC AGCGCCTGCC CGGCCGGGAG CACMACCCAC GGCCCTACTC CAGCGAAGTC 240

CCGCWCCGGC TTCTAGGRAT AAAGTTTACG TTYTCCTGAG GCCGCACCCC CCACYTCCCA 300

CCCAGGACGG CACATCTCCG TGTCYTCCTC CCCCAAAYTC CAYTMGGGAC CCCGAGAACC 360

ACCCCAGCYT TCCGGCCACC ACAACAAAGA GCCGCWCCGA CCGGCGAGGA TWAACAGCGG 420

CGGAGGGCGA KAGGGCGGCG GGGCGAGCGC CTCCACGCAG CAACTCCGGA GTCCCCCGCT 480

TGCCCGAGCG CAGTTTCTCC GCTGCTGTTT CCACCGGCTT TGTAACACTG GGAATTTACA 540

TCCTCACCCG CACCCCTCAC GCCCGAGGAT TTTAAACTCA CCTTTACTCT CGAACTGAGA 600

GTTGCGGTAG ATGGGATTTT TGCCTTTTCC CCAGATGGTT GAAGGTTAAG ATTTTTGGAA 660

ACCCCMCCAC CTCCTTATTT CTATTATTAT TTCTGCAAGA AAAGTATAAA GAGAGTTGTA 720

GTGGAGGTGA GATTTGTGAT CGGGAAAGCC TTCGACTCCC TCCTTCTCCG TCTTCCGCYT 780

CTCTCTCTCT GATTAGTTCC TATCCAGCAG CAGATTGAAG CAGGAGATGA TTCTTCTCAA 840

GGTTTGTTCA GCAGCTTCAC TTCTAGGCGA AGGCTTCATG AACCAAGTGA CGTCAACCAA 900

CAAGGCTTCT CTCTCTCTCC TCTCTCTAAC AATGAAAGTT GCTGTTAACA AGGGAAAAAA 960

AGAGAGAGAA TTGTTTATAC CATTTCAGTT CCAATAATAA AKGACCTATC AGYTCCTAAA 1020

GGAGCCAAAA AANANAAANA AAAAAAAAAA AANAAGANAA GNNNNNAAAA AAANAAAAAA 1080

AAA 1083

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Ile Leu Leu Lys Val Cys Ser Ala Ala Ser Leu Leu Gly Glu Gly
1 5 10 15

Phe Met Asn Gln Val Thr Ser Thr Asn Lys Ala Ser Leu Ser Leu Leu
20 25 30

Ser Leu Thr Met Lys Val Ala Val Asn Lys Gly Lys Lys Glu Arg Glu
35 40 45

Leu Phe Ile Pro Phe Gln Phe Gln
50 55

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 643 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GAAAGAGGAG CTGGGCGGGG TGGGGGGAAG GCGGAGGCAG TYTAGTAATG TAAAGCTCCG 60

CTGAGAGGGA GAGTGCCGCC CTAAACACTC ATGCTGCCAG TCCCCAAAAG ACTTCATTCA 120

TTCAACATAT ATGTGACCGC CTGCTACGTG CCAGGCGTGG GCCAGGTCCT AGGGACAAAG 180

GAGAGGCCTC CGCACCCCAC CCCATGACCC ATACCTCCTC TTCCCCACCT CCCTGGGCCA 240

GCCTGCCTTC CTTCTCCCTC CTCCTCCTTC CTGGGGGAAG GAAGCCCCAC CTTCTGTGCG 300

CAGTCAGCTC CTAAGCACGC TCCCGCTTCC CCTGGCCTCC CCATTTAAAA AGGGAGGCAA 360

AGGATGTCAC CACTGTCACT ACACTCATGG CTTTGCTCTG GGAAGTCCTG CAAATAAAAT 420

GAAAGTTCTC CAACCCCTCC MTACCCAYTC GGGCCACAAA GGCGAGGGGA GGCAGGTYTG 480

AGGCAGAGGA GCCAGGGCAG GTGCGGCGCT TCCGCYTCTG GTCCCAAAGC AAAGAKTCCC 540

CCTGTGACTG ACAGCCCGTG TTATGTTAAA TACATTTTGT TGGTTTGTAA TTCAAATCCC 600

ATAAAGCAGG AGGTAGAGAG CCAAAAAAAA AAAAAAAAAA AAA 643

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Leu Pro Val Pro Lys Arg Leu His Ser Phe Asn Ile Tyr Val Thr
1 5 10 15

Ala Cys Tyr Val Pro Gly Val Gly Gln Val Leu Gly Thr Lys Glu Arg
20 25 30

Pro Pro His Pro Thr Pro
35

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1047 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AGGCGATGCC CCATAAAAGG GCTCCTGAAG CTCTTTGTGA AGGGGTCTGA AAAGGGCAGA 60

TGAGGGTGTC CTTTGGGGCG GATGTGGGGT TTGGGACAAT TGCATGTGAT TGTCATTCTT 120

TAGCTGTCTG CATCCCACAG AAACTTTTTT CTGAGTCTTC CAGCTGGCCC AAGTCCTGGG 180

TCTCTTTTAC TGTTCTTGTA GCTGACTACA GTAGGCAGAT GAGGAACTCT TAGTCAATCT 240

GGGAAAACTC GACTGACTAT AAACAATCCT AAATTGAAAG AAGTGTATGG CATTGGGGGG 300

TGGGTGTGAT AGTACAGAGT GGAGCCTGCA AGTTCACGCA CCGGGAACCA AACCCCACCT 360

AACTTGGACT GGACGTCCTC TTCCAGGGAA TCCAGCCAGG GCCAATTAGA AATGTGTCTT 420

AAATTGGTGT CAGGTCACCA AAAACAAAAA CAGGATCCAT GGGGGCCTGT GAAACTTCGA 480

GTGCCATTCA TGCTCGGTTC AGTCATCTGA CTCGTCAGGA TGACCAGCAG TGCTCCCTGT 540

AACTCGCCAT TATCTGACCA ATTACTGGAG CTACTTTATA ATGAGGCTTC TGGAGCTACT 600

TTATAATGAG GCTTCTGTTT GCTGTCATGG TGGGGAGTTT GGAATTGTGG CTTCTTGCCT 660

AACACCAATG AGAGGACTTT GGGACAAACC CCCAGAGCCA GGAGTGTTTT GAGGCCTAGT 720

GGGGTTGGGA ACAAAGGGTC AAGTGTCGAG GGAGTGGGGA AATTATGGGT TGGGGACAGG 780

TGTGAACAGT GGGCTTGGGG GTGGCCCAAG AGTACTAGAC CAGAGAGGTC CAGTGCCACC 840

CGCAGCCTGC AGTGATACTA GACAGGGGGC GGCTGTGTGG AACCACAGAT GACATCCCTT 900

CTCCTCTTGA TGGAAGTGGA GGCTGCATCT GAGAGCTTCC CAGCCTAGAT TCTGGTGGCT 960

GCATCTGAGA GCTTCCCAGC CTAGATTCTG GTGGGATTGG ATCTGGGAGG GGGAAGACCC 1020

CAAAAAGCAA AAAAAAAAAA AAAAAAA 1047

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 57 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Met Arg Val Ser Phe Gly Ala Asp Val Gly Phe Gly Thr Ile Ala Cys
1 5 10 15

Asp Cys His Ser Leu Ala Val Cys Ile Pro Gln Lys Leu Phe Ser Glu
20 25 30

Ser Ser Ser Trp Pro Lys Ser Trp Val Ser Phe Thr Val Leu Val Ala
35 40 45

Asp Tyr Ser Arg Gln Met Arg Asn Ser
50 55

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2851 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

ATTTCGTACA GTAGGAGATT TCAACAACGT GACAATATTC TCTAGGCACT TGGGCTCACT 60

GTCTGTAGCC CCCACCCCCC GCCTTTCGCC ACCTCCTTGC TTCCCTACTC CCCCTTCTGC 120

TTTTGCCTTT GATGAGTTTT TGGCTTACTT TTTGGCGGAG TCTCTTGGAC ACGTTTTTGC 180

TGGTGCTGGA AGATCAGATA CATGGAACCT TTGAAAACTG ATTATTTTTC TCCGATATGA 240

CTTAAAAAAA AATAAAAAGA AGAAAAGAAA ATAGAGTAGT GCACGGCAAG CTAGAGGATT 300

GTAAATTTTC CTTGGTGAAC TTTGAGGATC CATAAAGAAG AAATGGTTCT CTTTACTGCG 360

AGGCTGCAAG GTCACCCAAT GAGAGAGGGG CCAAATAAGC TGGAACATCA TCTAATACAC 420

TGAATGTAGC CACTCTGTGT CTTTTGATTG GAGAGTTTAG TCCATTTACA TTCAATGCTA 480

TAATTGGAGT TACTGGAAAA GCAAGAATAA CTTATGCGGA TTAACAATAT GGAAACATCC 540

TGAGACTACT TTGGAATCGC CATAAATTAA GTGGGTTCCA GTTTTGCAAA CAGAGAAACG 600

GTCCATGAAC AATTTGCTAC AGGTATAAAG AAGTATCTGC AGAAATCCAG AGCACTTATT 660

AAACTTCTTT GAGTTTTCTC AGGAAGATCA ATACAAGATG GAGAAATTTT ATTAAGATTG 720

GCAAACGCAC TGCCTACTTA CAGCATAGAG ACCCCCAGTG GAGAGCTAGA CTGTTTGAAT 780

TCCAGAAGGA CCAACACCAG ATAAATTATG AATGTTGAAC AAGATGACCT TACATCCACA 840

GCAGATAATG ATAGGTCCTA GGTTTAACAG GGCCCTATTT GACCCCCTGC TTGTGGTGCT 900

GCTGGCTCTT CAACTTCTTG TGGTGGCTGG TCTGGTGCGG GCTCAGACCT GCCCTTCTGT 960

GTGCTCCTGC AGCAACCAGT TCAGCAAGGT GATTTGTGTT CGGAAAAACC TGCGTGAGGT 1020

TCCGGATGGC ATCTCCACCA ACACACGGCT GCTGAACCTC CATGAGAACC AAATCCAGAT 1080

CATCAAAGTG AACAGCTTCA AGCACTTGAG ACACTTGGAA ATCCTACAGT TGAGTAGGAA 1140

CCATATCAGA ACCATTGAAA TTGGGGCTTT CAATGGTCTG GCGAACCTCA ACACTCTGGA 1200

ACTCTTTGAC AATCGTCTTA CTACCATCCC GAATGGAGCT TTTGTATACT TGTCTAAACT 1260

GAAGGAGCTC TGGTTGCGAA ACAACCCCAT TGAAAGCATC CCTTCTTATG CTTTTAACAG 1320

AATTCCTTCT TTGCGCCGAC TAGACTTAGG GGAATTGAAA AGACTTTCAT ACATCTCAGA 1380

AGGTGCCTTT GAAGGTCTGT CCAACTTGAG GTATTTGAAC CTTGCCATGT GCAACCTTCG 1440

GGAAATCCCT AACCTCACAC CGCTCATAAA ACTAGATGAG CTGGATCTTT CTGGGAATCA 1500

TTTATCTGCC ATCAGGCCTG GCTCTTTCCA GGGTTTGATG CACCTTCAAA AACTGTGGAT 1560

GATACAGTCC CAGATTCAAG TGATTGAACG GAATGCCTTT GACAACCTTC AGTCACTAGT 1620

GGAGATCAAC CTGGCACACA ATAATCTAAC ATTACTGCCT CATGACCTCT TCACTCCCTT 1680

GCATCATCTA GAGCGGATAC ATTTACATCA CAACCCTTGG AACTGTAACT GTGACATACT 1740

GTGGCTCAGC TGGTGGATAA AAGACATGGC CCCCTCGAAC ACAGCTTGTT GTGCCCGGTG 1800

TAACACTCCT CCCAATCTAA AGGGGAGGTA CATTGGAGAG CTCGACCAGA ATTACTTCAC 1860

ATGCTATGCT CCGGTGATTG TGGAGCCCCC TGCAGACCTC AATGTCACTG AAGGCATGGC 1920

AGCTGAGCTG AAATGTCGGG CCTCCACATC CCTGACATCT GTATCTTGGA TTACTCCAAA 1980

TGGAACAGTC ATGACACATG GGGCGTACAA AGTGCGGATA GCTGTGCTCA GTGATGGTAC 2040

GTTAAATTTC ACAAATGTAA CTGTGCAAGA TACAGGCATG TACACATGTA TGGTGAGTAA 2100

TTCCGTTGGG AATACTACTG CTTCAGCCAC CCTGAATGTT ACTGCAGCAA CCACTACTCC 2160

TTTCTCTTAC TTTTCAACCG TCACAGTAGA GACTATGGAA CCGTCTCAGG ATGAGGCACG 2220

GACCACAGAT AACAATGTGG GTCCCACTCC AGTGGTCGAC TGGGAGACCA CCAATGTGAC 2280

CACCTCTCTC ACACCACAGA GCACAAGGTC GACAGAGAAA ACCTTCACCA TCCCAGTGAC 2340

TGATATAAAC AGTGGGATCC CAGGAATTGA TGAGGTCATG AAGACTACCA AAATCATCAT 2400

TGGGTGTTTT GTGGCCATCA CACTCATGGC TGCAGTGATG CTGGTCATTT TCTACAAGAT 2460

GAGGAAGCAG CACCATCGGC AAAACCATCA CGCCCCAACA AGGACTGTTG AAATTATTAA 2520

TGTGGATGAT GAGATTACGG GAGACACACC CATGGAAAGC CACCTGCCCA TGCCTGCTAT 2580

CGAGCATGAG CACCTAAATC ACTATAACTC ATACAAATCT CCCTTCAACC ACACAACAAC 2640

AGTTAACACA ATAAATTCAA TACACAGTTC AGTGCATGAA CCGTTATTGA TCCGAATGAA 2700

CTCTAAAGAC AATGTACAAG AGACTCAAAT CTAAAACATT TACAGAGTTA CAAAAAACAA 2760

ACAATCAAAA AAAAAGACAG TTTATTAAAA ATGACACAAA TGACTGGGCT AAATCTACTG 2820

TTTCAAAAAA GTGTCTTTAC AAAAAAAAAA A 2851

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 640 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Leu Asn Lys Met Thr Leu His Pro Gln Gln Ile Met Ile Gly Pro
1 5 10 15

Arg Phe Asn Arg Ala Leu Phe Asp Pro Leu Leu Val Val Leu Leu Ala
20 25 30

Leu Gln Leu Leu Val Val Ala Gly Leu Val Arg Ala Gln Thr Cys Pro
35 40 45

Ser Val Cys Ser Cys Ser Asn Gln Phe Ser Lys Val Ile Cys Val Arg
50 55 60

Lys Asn Leu Arg Glu Val Pro Asp Gly Ile Ser Thr Asn Thr Arg Leu
65 70 75 80

Leu Asn Leu His Glu Asn Gln Ile Gln Ile Ile Lys Val Asn Ser Phe

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                85                  90                  95

Lys His Leu Arg His Leu Glu Ile Leu Gln Leu Ser Arg Asn His Ile
            100                 105                 110

Arg Thr Ile Glu Ile Gly Ala Phe Asn Gly Leu Ala Asn Leu Asn Thr
        115                 120                 125

Leu Glu Leu Phe Asp Asn Arg Leu Thr Thr Ile Pro Asn Gly Ala Phe
    130                 135                 140

Val Tyr Leu Ser Lys Leu Lys Glu Leu Trp Leu Arg Asn Asn Pro Ile
145                 150                 155                 160

Glu Ser Ile Pro Ser Tyr Ala Phe Asn Arg Ile Pro Ser Leu Arg Arg
                165                 170                 175

Leu Asp Leu Gly Glu Leu Lys Arg Leu Ser Tyr Ile Ser Glu Gly Ala
            180                 185                 190

Phe Glu Gly Leu Ser Asn Leu Arg Tyr Leu Asn Leu Ala Met Cys Asn
        195                 200                 205

Leu Arg Glu Ile Pro Asn Leu Thr Pro Leu Ile Lys Leu Asp Glu Leu
    210                 215                 220

Asp Leu Ser Gly Asn His Leu Ser Ala Ile Arg Pro Gly Ser Phe Gln
225                 230                 235                 240

Gly Leu Met His Leu Gln Lys Leu Trp Met Ile Gln Ser Gln Ile Gln
                245                 250                 255

Val Ile Glu Arg Asn Ala Phe Asp Asn Leu Gln Ser Leu Val Glu Ile
            260                 265                 270

Asn Leu Ala His Asn Asn Leu Thr Leu Leu Pro His Asp Leu Phe Thr
        275                 280                 285

Pro Leu His His Leu Glu Arg Ile His Leu His His Asn Pro Trp Asn
    290                 295                 300

Cys Asn Cys Asp Ile Leu Trp Leu Ser Trp Trp Ile Lys Asp Met Ala
305                 310                 315                 320

Pro Ser Asn Thr Ala Cys Cys Ala Arg Cys Asn Thr Pro Pro Asn Leu
                325                 330                 335

Lys Gly Arg Tyr Ile Gly Glu Leu Asp Gln Asn Tyr Phe Thr Cys Tyr
            340                 345                 350

Ala Pro Val Ile Val Glu Pro Pro Ala Asp Leu Asn Val Thr Glu Gly
        355                 360                 365

Met Ala Ala Glu Leu Lys Cys Arg Ala Ser Thr Ser Leu Thr Ser Val
    370                 375                 380
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Ser Trp Ile Thr Pro Asn Gly Thr Val Met Thr His Gly Ala Tyr Lys
385                 390                 395                 400

Val Arg Ile Ala Val Leu Ser Asp Gly Thr Leu Asn Phe Thr Asn Val
                405                 410                 415

Thr Val Gln Asp Thr Gly Met Tyr Thr Cys Met Val Ser Asn Ser Val
            420                 425                 430

Gly Asn Thr Thr Ala Ser Ala Thr Leu Asn Val Thr Ala Ala Thr Thr
        435                 440                 445

Thr Pro Phe Ser Tyr Phe Ser Thr Val Thr Val Glu Thr Met Glu Pro
    450                 455                 460

Ser Gln Asp Glu Ala Arg Thr Thr Asp Asn Asn Val Gly Pro Thr Pro
465                 470                 475                 480

Val Val Asp Trp Glu Thr Thr Asn Val Thr Thr Ser Leu Thr Pro Gln
                485                 490                 495

Ser Thr Arg Ser Thr Glu Lys Thr Phe Thr Ile Pro Val Thr Asp Ile
            500                 505                 510

Asn Ser Gly Ile Pro Gly Ile Asp Glu Val Met Lys Thr Thr Lys Ile
        515                 520                 525

Ile Ile Gly Cys Phe Val Ala Ile Thr Leu Met Ala Ala Val Met Leu
    530                 535                 540

Val Ile Phe Tyr Lys Met Arg Lys Gln His His Arg Gln Asn His His
545                 550                 555                 560

Ala Pro Thr Arg Thr Val Glu Ile Ile Asn Val Asp Asp Glu Ile Thr
                565                 570                 575

Gly Asp Thr Pro Met Glu Ser His Leu Pro Met Pro Ala Ile Glu His
            580                 585                 590

Glu His Leu Asn His Tyr Asn Ser Tyr Lys Ser Pro Phe Asn His Thr
        595                 600                 605

Thr Thr Val Asn Thr Ile Asn Ser Ile His Ser Ser Val His Glu Pro
    610                 615                 620

Leu Leu Ile Arg Met Asn Ser Lys Asp Asn Val Gln Glu Thr Gln Ile
625                 630                 635                 640
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(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 4531 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TTGCTCTTCA ACTTTCTTTT GAGGCTTTAA ATTAGGCAAA TATATTTTTC TTAGAATTTC 60

TGAAAACTCC TTTTCACTGG AGCTTATTTT AATTATATGG ATGCATTATC CTCTTAAACT 120

TCTGTGAAAA CAATAATTGG AGTTTTCATT TGCATTGGCT GTTTCATGAG AGGTCAAGCT 180

TTTTGCTTAT TTATTTTGAT GTTTCCTTTT CATGATATCT GTGTCTTGGG ATTTGGTTGT 240

ATATTCACAT TTTTAATTAG CTACTTGATT TAAATAAAGT ATCAGTAGTT ACTTTCAGGG 300

TTCTTGGTGA TTATAATAAT TACTCACCTA CCAGGCTTCT TCCTTGCATG CAGCTCACTA 360

CAGGAATCTG TTGTGCCTAG AAGATTTCGG GACAAGTGGA GAAACCCCAC TCCGTTAACT 420

GCATACACAG GGAAGGAGCT ATGAGGGAGA CAGAATAATT TGGTCTCTAC TATTACCTTA 480

AGAGACCTTC CCCTGTCTTC GATTTAAAAA AAAACTACTG CATACAAAGG GTAGGAGCTA 540

CAAGGGACAT AGAATAATTT GGACTCCATT ACTACCTTAA GAGACCTTCC CCTGACTTCT 600

CTTTTAAAAA ACCTATGAGT CTCTGTACCC CTGAACTTAC TTTCCACACC TATTTCTCTC 660

TTCACCCCCA AAATCCATAT TAGAATGCCC CTGCAGGCTA TAAAGCCTTT CATAAAAGTA 720

AAATACCCAG TCTTTTCAAG AGAACAATAA AATAGGCAGT CTCCTACCTC TTGTCTTACT 780

CTAATATAAA CTCCATGAAG ATAAGTATTG TATCCATACT GTTCATGCTG CACAGCAGTT 840

GCCCTTATCT GCAGGGCGAC GCATCCCAAG ACCCCCAGTG GATGCTTGAA ACTGCAGAGA 900

GTAACACACG TGATTGCCAC CATCGGAACA CATTTCTGTT CACGTCTTCC ACCCACAGAT 960

TTAATGCCTT TTCCATCTTA ACTAAGCACT CATCATGGAC TGTGGCCATA ACTTTTGCAG 1020

TTTTAGATGC AACAGCAAAA CTAACATTAA TTTTTTCTTC TTCTTCACAA TTTCATGGGT 1080

AGATTTGTTC TTACCGTAGA TCTTAGCAAC CTCAGCATAT GATGTTTTTT CTTTTGAGAA 1140

CTTTCACCTT TTCTCTTAAA GAAATCACTT TACAGCTTCT CTTTGGCATA TCTCAACTGC 1200

CAGCATCACT GCTCTTGAAC TTTGGGGCCA TTATTAAGTC AAAAGAGGGT TACTTCAAAA 1260

CAAGCACTGA GATACCACCA GAGTCCATCT GATAACTAAG ATGGTAACTA CATGACTAAC 1320

AGGCCGGTGA CGTATAAAGC ATGGATATGC TGGACAAAGG GGTGAGTCAT ATCCCAGGTA 1380

GGATGAAGCA GGGTGACTTG AGATTTCACT ATTCAGTATG GTGCACAATT TAAAACTTAG 1440

GAATTGTTTA TTTCTTGGAA CTTTTCGTTT AATGTTTTTG GACTGCAGTT AGCCACAGGT 1500

AACTGAAACT GTGGAAAGTG AGGATTGGAG GATAAGCAGA GACTGTGGTA TTCATTTCAT 1560

TGCACAGTGC CTAAAATACA GTAGGTGTAC TATAAATATT TTGTAAAGGG ACAACTTTTC 1620

TGAAACTAAA AATATTTATG TTTTACCCAA TAATTTTTCT TCTGGAAATT TATGCTAAGG 1680

AAATATTCAG AGATGCTTAC AAAGTTTTAT GCATGAGTGT CCATGTTATT TGTAATTGTG 1740

AAAAATGAAA ATAACTCAAA AGTTTAACAG TGGTCATCTA AAGTATTGTA TACACTGTAT 1800

ATATAGGTTG AATAGAAGGT CATCCTATTC ATTTATTAAT GAGAGGTACA ATCTCTAGGG 1860

ATCTGTAAAA TCTATTTTGT CTTAACCAAA GAACAAATTT TTGACATATC TTGAATAGGA 1920

TGACTATAAA TTATGACTTT TAAATTGTTG TAATTTTTGT ACTATTATCT GATATTTTTA 1980

TTTTTATGTA TTTTCGTAAG TAGTTTAGAG ATAGTCACAT TTTAAAAATC TAAGATCAAG 2040

CAAATGAAGC TTATTTTTAT GTATTCATAG TATAAAAGAC CTTCAGTAAA TAGGTAATAT 2100

TTTTGTTTTA TTCTAGAAAA CAGCTCCTTG AACACAGTGA GCTGGCTTTT CACACATTGC 2160

AGTTGTTAGT GTTTACTGCC CTTGCCATTT TAATTATGAG GCTAAAGATG TTTTTGACAC 2220

CGCACATGTG TGTTATGGCT TCCTTGATAT GCTCTCGACA GCTCTTTGGC TGGCTTTTTC 2280

GCAGAGTTCG TTTTGAGAAG GTTATCTTTG GCATTTTAAC AGTGATGTCA ATACAAGGTT 2340

ATGCAAACCT CCGTAATCAA TGGAGCATAA TAGGAGAATT TAATAATTTG CCTCAGGAAG 2400

AACTTTTACA GTGGATCAAA TACAGTACCA CATCAGATGC TGTCTTTGCA GGTGCCATGC 2460

CTACAATGGC AAGCATCAAG CTGTCTACAC TTCATCCCAT TGTGAATCAT CCACATTACG 2520

AAGATGCAGA CTTGAGGGCT CGGACAAAAA TAGTTTATTC TACATATAGT CGAAAATCTG 2580

CCAAAGAAGT AAGAGATAAA TTGTTGGAGT TACATGTGAA TTATTATGTT TTAGAAGAGG 2640

CATGGTGTGT TGTGAGAACT AAGTTTATAC TTCAAGATGG ACAAGAAGTT CTATCAGCTG 2700

CTGAGAAATG ATGCCAGATG GTAACTCAGA TATACAAGAA ATACTCAAAT GCGCTGGAAA 2760

TGGCCTGGTT GCAGTATGCT TGAAATCTGG GATGTGGAAG ACCCTTCCAA TGCAGCTAAC 2820

CCTCCCTTAT GTAGCGTCCT GCTCGAAGAC GCCAGGCCTT ACTTCACCAC AGTATTTCAG 2880

AATAGTGTGT ACAGAGTATT GAAGGTTAAC TGAGAAGGAT ACTACCCATT TTACTATGGC 2940

ACAATGCCGT GTGTCAAAAA CAATCACCCT TTGGCTTATT CACATTAATA AAAATCACAA 3000

GCTTTAATAA CAGACACTTA AAAATAAGAT AAAAATGGAT TGGAAATTTT TCTGATTACT 3060

AAAAGGTAAA TTACTTTTCT GTTCATTGAA TGTCAGCCTT ATTAAGCTTG TCATATAAGT 3120

TATTAAATCA TTCATGTCAT ACTGCATAAA CAAATGTTCA TTTCAGAATT TTAAAGAGAA 3180

ATGTATATAA AAGAACAATG AATTTTAATA AATCAGGGGT ATGTAAGTCC TTTTTCATCC 3240

AACTAGGTGA ATTGCTTCAG ATTTTCTCTA GTACCAGAGG GTACCTCCTC AAACTCTTTG 3300

AACCACTTAA GGCAGAAGAA TGCAAGCTCT GAAATGACAT CCTTAAAATG CTGATACTGG 3360

TCACAGCCTC TTTACCTCTG TGAGGAAATT GTAACAGTGT GTCTTTTAAG GTGTTTTTAT 3420

TTTACCAGCC CTTAAGAAAG ATCTTTAATA CCTTTTAATA CTTTTTTTTA ATAATTTCAA 3480

GTTGAAGTGT TTTTAAAAAC ACTTTGTTTT GTAATGTTTT GAATCTCTTG AGATGTGTTT 3540

ACCCCACTAG ATACATATTT GCCACTGGTT AGTTCTCCAT CTAAGCTCAA GAGGTTATTC 3600

ATCTCTCTTT AGATTCCAGT GGTTTTTCTT TTAACATCCA GGTAAAATAG AAACTGCTAT 3660

GGTATACAAC CAAGTTTTGG GGTTAAACAT AATCAGAAAA GAAAATCCAG TTAAATTTAT 3720

GAAGTGAGAT TTTCAGATCC TAGATCTTGA ATAAAGGAAA GGTCTTTTCA TCTTGATGGC 3780

CCCAAAGCTT GTTGATCATG GTCTTTATTT CTGGCCACTA TCTTCTTAAA TAATATATTT 3840

TTAAGCCCTC ATTTATTTTT GGTTTTGGGT GAGGAAAGTC ATGTTTTCTA AGTCCTCTCC 3900

CCTAATAAAA CCTACCCAAC AATAGTGCTT TGAAAAGTGG TAGTTATCTT GAAGATACTC 3960

TTGCCAAATG CAAAGATAAA CATTCTTTTT GTCTGCTTTA TAAATATGAA ATATGCCAGA 4020

TCTGTAGTAT TTTAATGTGC ATCTACTTTA AATGAGTCAT CTTGGGGTTT TTATAATTCC 4080

CTTATGTTCT CGCCCCTCTA CACTTGAAAT AACAAAATGC CTTAATTTTA TGGATTAGTT 4140

CTCTTATAGT AGACAGGCAG CTATATGCAG CAAAACCAAT AAAGTTATTT TTCAACTTTC 4200

ATAGTTGTAA AATATTTTAT AACAGAATAC AAAACAGCTA AGAAAACATG CCACATTTTA 4260

TTTTAGCATT TTCAAATAAT TTGTTTTTGG TGTAAGCACA GGATAAAAAA GGAGAGCGTC 4320

AAAGAAAAGA GACATAACAC CTAACATTCA TAAAAATTAA CAAAGTATAT TTTGGATGAT 4380

GTTTTTACAG GAAATATTTT AAATAAGTTG GTAGAACTTT TAAAATGGTA CTGTATTAGC 4440

TAATAAAATA TTCAGTACAA ATATATGTTT GGATTTATGC ATTAAAAAAC TAATAAAATT 4500

ATTTCCAACT TTAAAAAAAA AAAAAAAAAA A 4531

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 171 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

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Met Arg Leu Lys Met Phe Leu Thr Pro His Met Cys Val Met Ala Ser
1               5                  10                  15

Leu Ile Cys Ser Arg Gln Leu Phe Gly Trp Leu Phe Arg Arg Val Arg
            20                  25                  30

Phe Glu Lys Val Ile Phe Gly Ile Leu Thr Val Met Ser Ile Gln Gly
        35                  40                  45

Tyr Ala Asn Leu Arg Asn Gln Trp Ser Ile Ile Gly Glu Phe Asn Asn
    50                  55                  60

Leu Pro Gln Glu Glu Leu Leu Gln Trp Ile Lys Tyr Ser Thr Thr Ser
65                  70                  75                  80

Asp Ala Val Phe Ala Gly Ala Met Pro Thr Met Ala Ser Ile Lys Leu
                85                  90                  95

Ser Thr Leu His Pro Ile Val Asn His Pro His Tyr Glu Asp Ala Asp
            100                 105                 110

Leu Arg Ala Arg Thr Lys Ile Val Tyr Ser Thr Tyr Ser Arg Lys Ser
        115                 120                 125

Ala Lys Glu Val Arg Asp Lys Leu Leu Glu Leu His Val Asn Tyr Tyr
    130                 135                 140

Val Leu Glu Glu Ala Trp Cys Val Val Arg Thr Lys Phe Ile Leu Gln
145                 150                 155                 160

Asp Gly Gln Glu Val Leu Ser Ala Ala Glu Lys
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1502 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCGACGGGA ACGTAGAACT CTCCAACAAT AAATACATTT GATAAGAAAG ATGGCTTTAA 60

AAGTGCTACT AGAACAAGAG AAAACGTTTT TCACTCTTTT AGTATTACTA GGCTATTTGT 120

CATGTAAAGT GACTTGTGAA ACAGGAGACT GTAGACAGCA AGAATTCAGG GATCGGTCTG 180

GAAACTGTGT TCCCTGCAAC CAGTGTGGGC CAGGCATGGA GTTGTCTAAG GAATGTGGCT 240

TCGGCTATGG GGAGGATGCA CAGTGTGTGA CGTGCCGGCT GCACAGGTTC AAGGAGGACT 300

GGGGCTTCCA GAAATGCAAG CCCTGTCTGG ACTGCGCAGT GGTGAACCGC TTTCAGAAGG 360

CAAATTGTTC AGCCACCAGT GATGCCATCT GCGGGGACTG CTTGCCAGGA TTTTATAGGA 420

AGACGAAACT TGTCGGCTTT CAAGACATGG AGTGTGTGCC TTGTGGAGAC CCTCCTCCTC 480

CTTACGAACC GCACTGTGCC AGCAAGGTCA ACCTCGTGAA GATCGCGTCC ACGGCCTCCA 540

GCCCACGGGA CACGGCGCTG GCTGCCGTTA TCTGCAGCGC TCTGGCCACC GTCCTGCTGG 600

CCCTGCTCAT CCTCTGTGTC ATCTATTGTA AGAGACAGTT TATGGAGAAG AAACCCAGCT 660

GGTCTCTGCG GTCACAGGAC ATTCAGTACA ACGGCTCTGA GCTGTCGTGT CTTGACAGAC 720

CTCAGCTCCA CGAATATGCC CACAGAGCCT GCTGCCAGTG CCGCCGTGAC TCAGTGCAGA 780

CCTGCGGGCC GGTGCGCTTG CTCCCATCCA TGTGCTGTGA GGAGGCCTGC AGCCCCAACC 840

CGGCGACTCT TGGTTGTGGG GTGCATTCTG CAGCCAGTCT TCAGGCAAGA AACGCAGGCC 900

CAGCCGGGGA GATGGTGCCG ACTTTCTTCG GATCCCTCAC GCAGTCCATC TGTGGCGAGT 960

TTTCAGATGC CTGGCCTCTG ATGCAGAATC CCATGGGTGG TGACAACATC TCTTTTTGTG 1020

ACTCTTATCC TGAACTCGCT GGAGAAGACA TTCATTCTCT CAATCCAGAA CTTGAAAGCT 1080

CAACGTCTTT GGATTCAAAT AGCAGTCAAG ATTTGGTTGG TGGGGCTGTT CCAGTCCAGT 1140

CTCATTCTGA AAACTTTACA GCAGCTACTG ATTTATCTAG ATATAACAAC ACACTGGTAG 1200

AATCAGCATC AACTCAGGAT GCACTAACTA TGAGAAGCCA GCTAGATCAG GAGAGTGGCG 1260

CTATCATCCA CCCAGCCACT CAGACGTCCC TCCAGGTAAG GCAGCGACTG GGTTCCCTGT 1320

GAACACAGCA CTGACTTACA GTAGATCAGA ACTCTGTTCC CAGCATAAGA TTTGGGGGAA 1380

CCTGATGAGT TTTTTTTTTG CATCTTTAAT AATTTCTTGT ATGTTGTAGA GTATGTTTTA 1440

AAATAAATTT CAAGTATTTT TTTTAAAAAC TAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1500

AA 1502

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 423 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Met Ala Leu Lys Val Leu Leu Glu Gln Glu Lys Thr Phe Phe Thr Leu
1               5                  10                  15

Leu Val Leu Leu Gly Tyr Leu Ser Cys Lys Val Thr Cys Glu Thr Gly
            20                  25                  30

Asp Cys Arg Gln Gln Glu Phe Arg Asp Arg Ser Gly Asn Cys Val Pro
        35                  40                  45

Cys Asn Gln Cys Gly Pro Gly Met Glu Leu Ser Lys Glu Cys Gly Phe
    50                  55                  60

Gly Tyr Gly Glu Asp Ala Gln Cys Val Thr Cys Arg Leu His Arg Phe
65                  70                  75                  80

Lys Glu Asp Trp Gly Phe Gln Lys Cys Lys Pro Cys Leu Asp Cys Ala
                85                  90                  95

Val Val Asn Arg Phe Gln Lys Ala Asn Cys Ser Ala Thr Ser Asp Ala
            100                 105                 110

Ile Cys Gly Asp Cys Leu Pro Gly Phe Tyr Arg Lys Thr Lys Leu Val
        115                 120                 125

Gly Phe Gln Asp Met Glu Cys Val Pro Cys Gly Asp Pro Pro Pro Pro
    130                 135                 140

Tyr Glu Pro His Cys Ala Ser Lys Val Asn Leu Val Lys Ile Ala Ser
145                 150                 155                 160

Thr Ala Ser Ser Pro Arg Asp Thr Ala Leu Ala Ala Val Ile Cys Ser
                165                 170                 175

Ala Leu Ala Thr Val Leu Leu Ala Leu Leu Ile Leu Cys Val Ile Tyr
            180                 185                 190

Cys Lys Arg Gln Phe Met Glu Lys Lys Pro Ser Trp Ser Leu Arg Ser
        195                 200                 205

Gln Asp Ile Gln Tyr Asn Gly Ser Glu Leu Ser Cys Leu Asp Arg Pro
    210                 215                 220
```

```
Gln Leu His Glu Tyr Ala His Arg Ala Cys Cys Gln Cys Arg Arg Asp
225                 230                 235                 240

Ser Val Gln Thr Cys Gly Pro Val Arg Leu Leu Pro Ser Met Cys Cys
                245                 250                 255

Glu Glu Ala Cys Ser Pro Asn Pro Ala Thr Leu Gly Cys Gly Val His
            260                 265                 270

Ser Ala Ala Ser Leu Gln Ala Arg Asn Ala Gly Pro Ala Gly Glu Met
        275                 280                 285

Val Pro Thr Phe Phe Gly Ser Leu Thr Gln Ser Ile Cys Gly Glu Phe
    290                 295                 300

Ser Asp Ala Trp Pro Leu Met Gln Asn Pro Met Gly Gly Asp Asn Ile
305                 310                 315                 320

Ser Phe Cys Asp Ser Tyr Pro Glu Leu Ala Gly Glu Asp Ile His Ser
                325                 330                 335

Leu Asn Pro Glu Leu Glu Ser Ser Thr Ser Leu Asp Ser Asn Ser Ser
            340                 345                 350

Gln Asp Leu Val Gly Gly Ala Val Pro Val Gln Ser His Ser Glu Asn
        355                 360                 365

Phe Thr Ala Ala Thr Asp Leu Ser Arg Tyr Asn Asn Thr Leu Val Glu
    370                 375                 380

Ser Ala Ser Thr Gln Asp Ala Leu Thr Met Arg Ser Gln Leu Asp Gln
385                 390                 395                 400

Glu Ser Gly Ala Ile Ile His Pro Ala Thr Gln Thr Ser Leu Gln Val
                405                 410                 415

Arg Gln Arg Leu Gly Ser Leu
            420
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 339 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
GCGGCCGCAG GTCTAGAATT CAATCGGGAG AGAGATACTG CCTGGTTCTT ACAGACACAG      60
```

ATTATGTCAT CCTTGCAGCC TTCACCCAAA GTTGCTCCCT CCTTCTAGGG CATTTTGTTT 120

TCCTACTTAA TACCAAGTGT CAGCATGTTA GTAATAAACA GGTGTCTCTA CCATTAGTCA 180

AAGGTGGGAG TTAAGCCTTT CATCTTTGTA GCTTTCTCCA GTACCTAACC ATGATTTACT 240

TCATGGGAAG TCCCTCAAAG TACTATTAAT TATCCTGTGT TCTCCTGCCT TGCCTCTTAA 300

CAAAAATTCT GCTGTTCCTG ATTATTTCCA TTTTACCAG 339

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 552 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

AAATANAAAT ANAACAAATT NTAGGGAAGG ACTAAACTGT CTAAAGAAAT GTAAAATCCA 60

AAGACTTGGA TTTTCAACCT ATATCAGAAG ACACTTTTTT TTCAGTTCCC ATGTGAAATT 120

CTTTNTAGGC CAAGGAAGGA CAAATACAAA TTTTGATTAC AAATTATTTT TAGAACTTTG 180

ACACCTACAC TTAAATTCTG AGTCATTAAA CAGGCCTACA TTTATCAACT GTGGAAATAT 240

CAGCCAGTTT TTGCAAACCT CTTCTTAGGA CACTAAGTTG TTTGCAGAAA TCACTAGCAT 300

TGACTGACTC AGCAACAATG TGGTTATATT CTTTGATTAA CTTAGTCCTT TTTCTTGGTC 360

AAGAGTCAGT AGACAGGACT GAAGCTTATG CCCCTTGCCC CCCCACCACC ACTCCATTAC 420

TACCACCTTG GTTTAGCCAT CCTTTTCTTG ATCTGTTCTC CCCACTTCTA CTGTGCTACT 480

CTACAGACTT GCCCTGAATG TAAGAGCAAC AATTACCTTG TAAAGTCCAA GTTGGGGCAG 540

GTCACTCCCA AA 552

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Thr Gly Leu His Leu Ser Thr Val Glu Ile Ser Ala Ser Phe Cys Lys
1 5 10 15

Pro Leu Leu Arg Thr Leu Ser Cys Leu Gln Lys Ser Leu Ala Leu Thr
20 25 30

Asp Ser Ala Thr Met Trp Leu Tyr Ser Leu Ile Asn Leu Val Leu
35 40 45

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TTTTTTNGGA ATCACCAAAA TCAAGNGNGA TATTGTGTTT GCTGCCAGCC TNNANTTGTA 60

GAGTCAGCTA AAGGAATGTG NGATTTTAAA TTATTGACCA CCTGTTTGAT TACAGTTGAN 120

NACAAATGCC TGCAAGTGTG GATTTGGTTT TCCCANACAT TTTAATATGT ATTATATTTA 180

AATCAAACAT CATTCATAGA AAGCATATNA CANANATGTT TANACATAAG CATNACATTT 240

TTTTAATAAA AATGTANACA GGTGGGGCAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 300

AAAAAAAA 308

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 789 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CTCTCCTCTG GCTACTGGGT GCTCGTGGTG CATTTTACTC GGAGAGAGGC CATCAAGCAG 60

ATCGAGGTGC TGCAGCACGT GGCCACCAAC CTGGGGCGCA GCCGTGCCTG GCTGTACCTG 120

GCCCTCAACG ARAACTCCCT TGGARARACT ACCTGCGGTT GTTCCARGAR AAACCTGGGC 180

CTGCTGCATA AGTACTACGT CAAGAATGCC CTGGTCTGCA GCCACGATCA CCTGACGCTC 240

TTCCTGACCT TGGTGTCCGG GCTAGAGTTC ATTCGTTTCG AGCTGGATCT GGATGCCCCT 300

TACCTAGACC TGGCCCCCTA CATGCCCGAC TACTACAAAC CTCAGTACCT GCTGGACTTT 360

GAAGACCGCC TTCCCAGCTC GGTCCACGGC TCAGACAGTC TGTCCCTCAA CTCTTTCAAC 420

TCCGTCACCT CCACCAACCT GGAGTGGGAT GACAGTGCGA TTGCCCCATC TAGTGAGGAT 480

TATGATTTTG GAGATGTGTT TCCAGCAGTG CCGTCTGTAC CCAGCACAGA CTGGGAAGAT 540

GGAGACCTCA CAGACACGGT CAGTGGTCCC CGCTCCACAG CCTCCGACCT GACCAGCAGC 600

AAGGCCTCCA CCAGGAGCCC CACCCAGCGC CAGAACCCCT TCAACGAGGA GCCGGCAGAG 660

ACTGTGTCCT CCTCTGACAC CACCCCCGTG CACACCACCT CTCAGGAGAA GGAGGAGGCC 720

CAGGCCCTGG ACCCGCCGGA TGCCTGCACG GAGCTCGAGG TCATCAGGGT CACCAAAAAA 780

AAAAAAAAA 789

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Pro Asp Tyr Tyr Lys Pro Gln Tyr Leu Leu Asp Phe Glu Asp Arg
1 5 10 15

Leu Pro Ser Ser Val His Gly Ser Asp Ser Leu Ser Leu Asn Ser Phe
20 25 30

Asn Ser Val Thr Ser Thr Asn Leu Glu Trp Asp Asp Ser Ala Ile Ala
35 40 45

Pro Ser Ser Glu Asp Tyr Asp Phe Gly Asp Val Phe Pro Ala Val Pro
50 55 60

```
Ser Val Pro Ser Thr Asp Trp Glu Asp Gly Asp Leu Thr Asp Thr Val
65                  70                  75                  80

Ser Gly Pro Arg Ser Thr Ala Ser Asp Leu Thr Ser Ser Lys Ala Ser
                85                  90                  95

Thr Arg Ser Pro Thr Gln Arg Gln Asn Pro Phe Asn Glu Glu Pro Ala
            100                 105                 110

Glu Thr Val Ser Ser Ser Asp Thr Thr Pro Val His Thr Thr Ser Gln
        115                 120                 125

Glu Lys Glu Glu Ala Gln Ala Leu Asp Pro Pro Asp Ala Cys Thr Glu
    130                 135                 140

Leu Glu Val Ile Arg Val Thr
145                 150
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3443 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
AGAGACCCAA AGCCAAAACT CAGCTGACAG GAATGTTTCA AAGGACACAA AGAGAGATGT     60

GGACTCAAAG TCACCGGGGA TGCCTTTATT TGAAGCAGAG GAAGGAGTTC TATCACGAAC    120

CCAGATATTT CCTACCACTA TTAAAGTCAT TGATCCAGAA TTTCTGGAGG AGCCACCTGC    180

ACTTGCATTT TTATATAAGG ATCTGTATGA AGAAGCAGTT GGAGAGAAAA AGAAGGAAGA    240

GGAGACAGCT TCTGAAGGTG ACAGTGTGAA TTCTGAGGCA TCATTTCCCA GCAGAAATTC    300

TGACACTGAT GATGGAACAG GAATATATTT TGAGAAGTAC ATACTCAAAG ATGACATTCT    360

CCATGACACA TCTCTAACTC AAAAGGACCA GGGCCAAGGT CTGGAARAAA AACRAGTTGG    420

TAAGGATGAT TCATACCAAC CGATAGCTGC AGAAGGGGAA ATTTGGGGAA AGTTTGGAAC    480

TATTTGCAGG GAGAAGAGTC TGGAAGAACA GAAAGGTGTT TATGGGGAAG GAGAATCAGT    540

AGACCATGTG GAGACCGTTG GTAACGTAGC GATGCAGAAG AAAGCTCCCA TCACAGAGGA    600

CGTCAGAGTG GCTACCCAGA AAATAAGTTA TGCGGTTCCA TTTGAAGACA CCCATCATGT    660
```

TCTGGAGCGT GCAGATGAAG CAGGCAGTCA GGGTAATGAA GTCGGAAATG CAAGTCCAGA 720

GGTCAATCTG AATGTCCCAG TACAAGTGTC CTTCCCGGAG GAAGAATTTG CATCTGGTGC 780

AACTCATGTT CAAGAAACAT CACTAGAAGA ACCTAAAATC CTGGTCCCAC CTGAGCCAAG 840

TGAAGAGAGG CTCCGTAATA GCCCTGTTCA GGATGAGTAT GAATTTACAG AATCCCTGCA 900

TAATGAAGTG GTTCCTCAAG ACATATTATC AGAAGAACTG TCTTCAGAAT CCACACCTGA 960

AGATGTCTTA TCTCAAGGAA AGGAATCCTT TGAGCACATC AGTGAAAATG AATTTGCGAG 1020

TGAGGCAGAA CAAAGTACAC CTGCTGAACA AAAAGAGTTG GGCAGCGAGA GGAAAGAAGA 1080

AGACCAATTA TCATCTGAGG TAGTAACTGA AAAGGCACAA AAAGAGCTGA AAAAGTCCCA 1140

GATTGACACA TACTGTTACA CCTGCAAATG TCCAATTTCT GCCACTGACA AGGTGTTTGG 1200

CACCCACAAA GACCATGAAG TTTCAACGCT TGACACAGCT ATAAGTGCTG TAAAGGTTCA 1260

ATTAGCAGAA TTTCTAGAAA ATTTACAAGA AAAGTCCTTG AGGATTGAAG CCTTTGTTAG 1320

TGAGATAGAA TCCTTTTTTA ATACCATTGA GGAAAACTGT AGTAAAAATG AGAAAAGGCT 1380

AGAAGAACAG AATGAGGAAA TGATGAAGAA GGTTTTAGCA CAGTATGATG AGAAAGCCCA 1440

GAGCTTTGAG GAAGTGAAGA AGAAGAAGAT GGAGTTCCTG CATGAGCAGA TGGTCCACTT 1500

TCTGCAGAGC ATGGACACTG CCAAAGACAC CCTGGAGACC ATCGTGAGAG AAGCAGAGGA 1560

GCTTGATGAG GCCGTCTTCC TGACTTCGTT TGAGGAAATC AATGAAAGGT TGCTTTCTGC 1620

AATGGAGAGC ACTGCTTCTT TAGAGAAAAT GCCTGCTGCG TTTTCCCTTT TTGAACATTA 1680

TGATGACAGC TCGGCAAGAA GTGACCAGAT GTTAAAACAA GTGGCTGTTC CACAGCTTCC 1740

TAGATTAGAA CTCAGGAACC AAATTTTGCC ACCAGCACAA CAATTGCAGT TTACTGGAGC 1800

ATGAACAAGG AAGATGTCAT TGATTCATTT CAGGTTTACT GCATGGAGGA GCCACAAGAT 1860

GATCAAGAAG TAAATGAGTT GGTAGAAGAA TACAGACTGA CAGTGAAAGA AAGCTACTGC 1920

ATTTTTGAAG ATCTGGAACC TGACCGATGC TATCAAGTGT GGGTGATGGC TGTGAACTTC 1980

ACTGGATGTA GCCTGCCCAG TGAAAGGGCC ATTTTTAGGA CAGCACCCTC CACCCCTGTG 2040

ATCCGCGCTG AGGACTGTAC TGTGTGTTGG AACACAGCCA CTATCCGATG GCGGCCCACC 2100

ACCCCAGAGG CCACGGAGAC CTACACTCTG GAGTACTGCA GACAGCACTC TCCTGAGGGA 2160

GAGGGCCTCA GATCTTTCTC TGGAATCAAA GGACTCCAGC TGAAAGTTAA CCTCCAACCC 2220

AATGATAACT ACTTTTTTTA TGTGAGGGCC ATCAATGCAT TTGGGACAAG TGAACAGAGT 2280

GAAGCTGCTT TCATCTCCAC CAGAGGAACC AGATTTCTCT TGTTGAGAGA AACAGCTCAT 2340

CCTGCTCTAC ACATTTCCTC AAGTGGGACA GTGATCAGCT TTGGTGAGAG GAGACGGCTG 2400

ACGGAAATCC CGTCAGTGCT GGGTGAGGAG CTGCCTTCCT GTGGCCAGCA TTACTGGGAA 2460

ACCACAGTCA CAGACTGCCC AGCATATCGA CTCGGCATCT GCTCCAGCTC GGCTGTGCAG 2520

GCAGGTGCCC TAGGACAAGG GGAGACCTCA TGGTACATGC ACTGCTCTGA GCCACAGAGA 2580

TACACATTTT TCTACAGTGG TATTGTGAGT GATGTTCATG TGACTGAGCG TCCAGCCAGA 2640

GTGGGCATCC TGCTGGACTA CAACAACCAG AGATTATCTT CATCAACGCA GAGAGCGAGC 2700

AGTTGCTCTT CATCATCAGG CACAGGTTTA ATGAGGGTGT CCACCCTGCC TTTGCCCTGG 2760

AGAAACCTGG AAAATGTACT TTGCACCTGG GGATAGAGCC CCCGGATTCT GTAAGGCACA 2820

AGTGATCCTT GGCTTTCAGA ATTTGCAAGA ACAGCGATTT GAATTTTGGG GGGGTCTGCT 2880

GTTCATTCCT TTAGGTGCTA TACATTATTC AAAAAGTCTC CCGCGCATTT GCACTAATGA 2940

TGGCTGCATG CATAGCAATC AGCATGTGAG CAAAATCGAC AAGAAAACCT TGACTTTACA 3000

GAGCAGTGTG TGAGTAAACA GAATGAAAAC AACAACCTCC ACTCTTTAGT TTATATAAGT 3060

TTGAGTTCTT TCCTAAATTA AAAGATCTAC ACTTGAGTTG GGAACCGAAA GAGAAAAATG 3120

GACTTCCATC TGTTTTACTG GTAAAGGAAA TCCTCTGATG GACAGGTCAG AGTGAAGGAA 3180

GGTTGTGCTG GTAAGACATC TCTGACGAAG AGCCATGGAT GCTTTCCACA AAATGTCACC 3240

TCGCTGCACT AAAGGATGAT GAATCCTAAT CATTAAAGGA ATTGTTTCAG CTGATTTAAA 3300

TTTATAATGA ACTCTTTTGT AATAATGTAT ACTGTAGAAC ATGAGTCTCT CCTCCCTAAA 3360

ATTTTAAATG TAGAAAAGTG CTATATATTA GAAATTTCCA TTTTGTTAAA TAAATGGTTA 3420

GAGTCTATAA AAAAAAAAAA AAA 3443

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 574 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Pro Leu Phe Glu Ala Glu Glu Gly Val Leu Ser Arg Thr Gln Ile
1 5 10 15

```
Phe Pro Thr Thr Ile Lys Val Ile Asp Pro Glu Phe Leu Glu Glu Pro
            20                  25                  30

Pro Ala Leu Ala Phe Leu Tyr Lys Asp Leu Tyr Glu Glu Ala Val Gly
        35                  40                  45

Glu Lys Lys Lys Glu Glu Glu Thr Ala Ser Glu Gly Asp Ser Val Asn
    50                  55                  60

Ser Glu Ala Ser Phe Pro Ser Arg Asn Ser Asp Thr Asp Asp Gly Thr
65                  70                  75                  80

Gly Ile Tyr Phe Glu Lys Tyr Ile Leu Lys Asp Asp Ile Leu His Asp
                85                  90                  95

Thr Ser Leu Thr Gln Lys Asp Gln Gly Gln Gly Leu Glu Xaa Lys Xaa
            100                 105                 110

Val Gly Lys Asp Asp Ser Tyr Gln Pro Ile Ala Ala Glu Gly Glu Ile
        115                 120                 125

Trp Gly Lys Phe Gly Thr Ile Cys Arg Glu Lys Ser Leu Glu Glu Gln
    130                 135                 140

Lys Gly Val Tyr Gly Glu Gly Glu Ser Val Asp His Val Glu Thr Val
145                 150                 155                 160

Gly Asn Val Ala Met Gln Lys Lys Ala Pro Ile Thr Glu Asp Val Arg
                165                 170                 175

Val Ala Thr Gln Lys Ile Ser Tyr Ala Val Pro Phe Glu Asp Thr His
            180                 185                 190

His Val Leu Glu Arg Ala Asp Glu Ala Gly Ser Gln Gly Asn Glu Val
        195                 200                 205

Gly Asn Ala Ser Pro Glu Val Asn Leu Asn Val Pro Val Gln Val Ser
    210                 215                 220

Phe Pro Glu Glu Glu Phe Ala Ser Gly Ala Thr His Val Gln Glu Thr
225                 230                 235                 240

Ser Leu Glu Glu Pro Lys Ile Leu Val Pro Pro Glu Pro Ser Glu Glu
                245                 250                 255

Arg Leu Arg Asn Ser Pro Val Gln Asp Glu Tyr Glu Phe Thr Glu Ser
            260                 265                 270

Leu His Asn Glu Val Val Pro Gln Asp Ile Leu Ser Glu Glu Leu Ser
        275                 280                 285

Ser Glu Ser Thr Pro Glu Asp Val Leu Ser Gln Gly Lys Glu Ser Phe
    290                 295                 300

Glu His Ile Ser Glu Asn Glu Phe Ala Ser Glu Ala Glu Gln Ser Thr
```

```
305                 310                 315                 320

Pro Ala Glu Gln Lys Glu Leu Gly Ser Glu Arg Lys Glu Glu Asp Gln
                325                 330                 335

Leu Ser Ser Glu Val Val Thr Glu Lys Ala Gln Lys Glu Leu Lys Lys
            340                 345                 350

Ser Gln Ile Asp Thr Tyr Cys Tyr Thr Cys Lys Cys Pro Ile Ser Ala
        355                 360                 365

Thr Asp Lys Val Phe Gly Thr His Lys Asp His Glu Val Ser Thr Leu
    370                 375                 380

Asp Thr Ala Ile Ser Ala Val Lys Val Gln Leu Ala Glu Phe Leu Glu
385                 390                 395                 400

Asn Leu Gln Glu Lys Ser Leu Arg Ile Glu Ala Phe Val Ser Glu Ile
                405                 410                 415

Glu Ser Phe Phe Asn Thr Ile Glu Glu Asn Cys Ser Lys Asn Glu Lys
            420                 425                 430

Arg Leu Glu Glu Gln Asn Glu Glu Met Met Lys Lys Val Leu Ala Gln
        435                 440                 445

Tyr Asp Glu Lys Ala Gln Ser Phe Glu Glu Val Lys Lys Lys Lys Met
    450                 455                 460

Glu Phe Leu His Glu Gln Met Val His Phe Leu Gln Ser Met Asp Thr
465                 470                 475                 480

Ala Lys Asp Thr Leu Glu Thr Ile Val Arg Glu Ala Glu Glu Leu Asp
                485                 490                 495

Glu Ala Val Phe Leu Thr Ser Phe Glu Glu Ile Asn Glu Arg Leu Leu
            500                 505                 510

Ser Ala Met Glu Ser Thr Ala Ser Leu Glu Lys Met Pro Ala Ala Phe
        515                 520                 525

Ser Leu Phe Glu His Tyr Asp Asp Ser Ser Ala Arg Ser Asp Gln Met
    530                 535                 540

Leu Lys Gln Val Ala Val Pro Gln Leu Pro Arg Leu Glu Leu Arg Asn
545                 550                 555                 560

Gln Ile Leu Pro Pro Ala Gln Gln Leu Gln Phe Thr Gly Ala
                565                 570
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1199 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

RGACTTGTTG CCAGTGATAC CAAAACAGAC TTTTCCCAAG CAGTGCCTCA CATGTCTGCT 60

GGTGTGGCTT TGGGATTCTC CTGCCCCACC CCCCCGTCCA TGGCAGCCCC CTCCCCAAGG 120

CTTTGCTCAC ACCTGAGACA GGAAGGAGGA AGGGGATCCA ATAGGAATAT GGGCCCCGGA 180

GGGGAAGTCA TGCACCCCCA AGCCACCACC CCCCAGCCTT CCACGCACAT CTCCTGGYTG 240

GAAGAGAGCC CTCCAAAAAG GGGACACAGG CTGCCCCGGC CCCTCAACTG CATCCACACC 300

CCATCCTCTC ATCTTGGGTC CCAGCCAGGC CCCCCCAAAA CCAAAGCCCC CTCAAGTCCT 360

GGGGTCCCAG CCTGTGCCCC CAGCTTCCTG CCCACCCAGC CCTGAGCATT CTCACACAGA 420

GAAAGAACAA GCAAGGGCTC CAGGGGGACA GGATGGGGCA GGGCATACAG TGGGGGGTGG 480

GGGGGCAGCT GGGAGGAGGG AGGGACAAAA CAAAACATTT TCCTTTGGGT TTTTTTTTTC 540

TTTCTTTTTT CTCCCCTTTA CTCTTTGGGT GGTGTTGCTT TTCCTTTCCT TTTCCCTTTG 600

AGATTTTTTT GTTGTTGTTT CCTTTTTGTA TTTTACTGAT ATCACCAGGA TAGTTTACTC 660

TCCTTCTAGC TTTCTGCTTA CCGCACACTG GATAACACAC ACATACACAC CCACAAAAAT 720

GCTCATGAAC CCAATCCGGA GAAGGTTCCA GCAGGTCCCC CACCCTCCCC TCCTCCTCCT 780

ACTTCTCCTC TTGACAGCGA GGACAGGAGG GGGACAAGGG GACACCTGGG CAGACCCGCC 840

GGCTCTCCCC CCACCCCACC CCGCCCCTCA CATCATACTC CAATCATAAC CTTGTATATT 900

ACGCAGTCAT TTTGGTTTTC GCGGACGCGC CTACCTAAGT ACCATTTACA GAAAGTGACT 960

CTGGCTGTCA TTATTTTGTT TATTTGTTCC CTATGCAAAA AAAAAATGAA AATGAAAAAA 1020

GGGGGATTCC ATAAAAGATT CAATAAAAGA CAAACAAAAA AAAAAGAAAA AAGAAAAAAA 1080

TGTATAAAAA TTAAACAAGC TATGCTTCGA CTCAAAAAAA AAAAAAAAAA AAAAAAAAAA 1140

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAA 1199

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Leu Met Asn Pro Ile Arg Arg Arg Phe Gln Gln Val Pro His Pro
1 5 10 15

Pro Leu Leu Leu Leu Leu Leu Leu Leu Thr Ala Arg Thr Gly Gly Gly
20 25 30

Gln Gly Asp Thr Trp Ala Asp Pro Pro Ala Leu Pro Pro Pro His Pro
35 40 45

Ala Pro His Ile Ile Leu Gln Ser
50 55

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 839 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GAATGAAAAT CCAGGTGTTT GTCATTCATC AGCAACAGGT GATCCCCATT GCAGGCAGCC 60

GGAACCGACG TCTCCTGGAC CACTGAGCTG GCTGTTCTCA TTACTGCCCT TTCCGCCCAG 120

GCTGGCGGTG ACTCACCGTG AGACAAGTCA GCTAGGTGTT CAGGACAGGG ATTTCAGAGT 180

ATTTTTGTCC AAAGAGGAAA GGGATGATTT CTACGGATCA CTACCAGTTG GTTTACTGTT 240

AGCTNCATCG TGTTGATCAC ACCAAGTCCT TGCCAATTTG GTTTTCTAAG TATTTTCACG 300

CCTTCTCCTC GTGTCCGCGT CACTGCTCTG ATTCAGGCCC TTGTCATTTC TCATCTTTGC 360

CATTTTAGTA GTTTTTGGAT TGGGCTCCCG GCTGCTAATT TTGTCCCCTT TTCCACTATC 420

TTCCACATTG TCACCGCAGT CATGTTTCTA AGGCAGAATC TCACTGTGCC CCTCATCGTG 480

TTGGGTGACT TSTGGTGGCA TCCCGTCACC CTCAGGACAA CCTTTCCTGG GGCCTGCCCG 540

CTCTGCTCTT GCTGCTGCCT CGCTGTCCCC CTCCTCCCTC CTGTGGTTTA TATTCCAGGA 600

ATTCTGAATT AGTTGCACCG TGCTCTCATA TTTACTGCAA GAATAGACCA GTGGTTCTCC 660

AGCTTTTCTG CACTCTGGAA TCACCTGGGG GTCTTTAAAA AACACTGCCT GGCTCCTAGT 720

CCTAAATTTG GAGATTTAAC TGGACTTACA GTTTTTCAAA GCACCCCAAA AGATTCTAAT 780

GTGCAGCAAA GTTTGGGAAC CACTGGTATA GACTGTCTTC TGCTTGTTTT CTTGAAAAA 839

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 56 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Phe Leu Arg Gln Asn Leu Thr Val Pro Leu Ile Val Leu Gly Asp
1 5 10 15

Xaa Trp Trp His Pro Val Thr Leu Arg Thr Thr Phe Pro Gly Ala Cys
20 25 30

Pro Leu Cys Ser Cys Cys Cys Leu Ala Val Pro Leu Leu Pro Pro Val
35 40 45

Val Tyr Ile Pro Gly Ile Leu Asn
50 55

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ANTATCCCAC CAGCTTCTCA CAGGTGTCA 29

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GNAGGCATCA CTGTGGCTAT TTCAATCTC 29

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

TNCCATCTAC CGCAACTCTC AGTTCGAGA 29

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TNAGTGTAGT GACAGTGGTG ACATCCTTT 29

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

TGAAGGGGTC TGAAAAGGGC AGATGAG 27

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

TNTTGGTGGA GATGCCATCC GGAACCTCA 29

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GNTCTTGGGA TGCGTCGCCC TGCAGATAA 29

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonculeotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GNAAGCCGAC AAGTTTCGTC TTCCTATAA 29

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GNTAAACCAA GGTGGTAGTA ATGGAGTGG 29

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GNTTGGTGGA GGTGACGGAG TTGAAAGAG 29

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GNCTCCTCCA GAAATTCTGG ATCAATGAC 29

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

TCCTCCTACT TCTCCTCTTG ACAGCGA 27

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

TNCCTTAGAA ACATGACTGC GGTGACAAT 29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22034

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 21/04; C07K 14/705; C12N 15/09, 15/63; C12Q 1/68

US CL : 536/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.3; 435/7.2, 69.1, 320.1; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, MEDLINE, JAPIO, SCISEARCH, WPIDS, EMBASE, EMBL-EST55, EMBL55, N-GENESEQ32, N-ISSUED, PIR
search terms: atcc 98101, ac41_1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	Database GENBANK on STN, National Institute of Health, Accession No. L20319, PFEIFFER, S.S. Rattus Norvegicus Developmentally Regulated Protein mRNA, Complete cds, Emb153 Database. 30 June 1993.	1 ---- 2-12
Y	WO 94/01548 A2 (MEDICAL RESEARCH COUNCIL) 20 January 1994, see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 JANUARY 1999	Date of mailing of the international search report 01 FEB 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer NIRMAL S. BASI Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)☆

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22034

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-13

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/22034

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-13, drawn to clone AC41-1 encoding the protein of SEQ ID NO:2.
Group II, claim(s)14-16, drawn to clone AC222-1 encoding the protein of SEQ ID NO:4.
Group III, claim(s)17-19, drawn to clone AJ143-1 encoding the protein of SEQ ID NO:6.
Group IV, claim(s)20-22, drawn to clone AC168-1 encoding the protein of SEQ ID NO:8.
Group V, claim(s)23-25, drawn to clone AK684-1 encoding the protein of SEQ ID NO:10.
Group VI, claim(s)26-28, drawn to clone AS209-1 encoding the protein of SEQ ID NO:12.
Group VII, claim(s)29-31, drawn to clone AX56-28 encoding the protein of SEQ ID NO:14.
Group VIII, claim(s)32-34, drawn to clone AX92-3 encoding the protein of SEQ ID NO:16.
Group IX, claim(s)35-37, drawn to clone BF245-1 encoding the protein of SEQ ID NO:19.
Group X, claim(s)38-40, drawn to clone B633-7 encoding the protein of SEQ ID NO:22.
Group XI, claim(s)41-43, drawn to clone BM46-10 encoding the protein of SEQ ID NO:24.
Group XII, claim(s)44-46, drawn to clone J317-1 encoding the protein of SEQ ID NO:26.
Group XIII, claim(s)47-49, drawn to clone O289-1 encoding the protein of SEQ ID NO:28.

The inventions listed as Groups I-XIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is directed to polynucleotide and polypeptide disclosed in SEQ ID NO:1 and SEQ ID NO:2 and present in clone AC41-1, allelic variants, polynucleotides capable of hybridizing to said polynucleotide sequence, host cells transformed with said polynucleotide, isolated gene containing said polynucleotide and method for preventing, treating or ameliorating a medical condition using said polypeptide. The special technical feature of Group I is the polypeptide and polynucleotide disclosed in SEQ ID NO:1 and SEQ ID NO:2. Groups II-XIII do not share the special technical feature of Group I, instead they are directed to a other polypeptide and polynucleotides structurally different to those of Group I.